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TABLE OF CONTENTS

Abstract:

Background: Obesity is caused by an imbalance between energy intake, i.e., eating, and energy expenditure (EE). Severe obesity is more prevalent in women than men worldwide, and obesity pathophysiology and the resultant obesity-related disease risks differ in women and men. The underlying mechanisms are largely unknown. Pre-clinical and clinical research indicate ovarian hormones may play a major role.

Rationale/Objectives: We systematically reviewed the clinical and pre-clinical literature on the effects of ovarian hormones on the physiology of adipose tissue (AT) and the regulation of AT mass by energy intake (i.e., eating) and EE.

Outcomes: We find that estrogens play a leading role in the causes and consequences of female obesity. With respect to adiposity, estrogens synergize with AT genes to increase gluteofemoral subcutaneous AT mass and decrease central AT mass in reproductive-age women, which leads to protective cardiometabolic effects. Loss of estrogens after menopause, independent of aging, increases total AT and decreases lean body mass, so that there is little net effect on body weight. Menopause also partially reverses women's protective AT distribution. These effects can be counteracted by estrogen treatment. With respect to eating, increasing estrogen levels progressively decrease eating during the follicular and peri-ovulatory phases of the menstrual cycle. Progestin levels are associated with eating during the luteal phase, but there does not appear to be a causal relationship. Progestins may increase binge-eating and eating stimulated by negative emotional states during the luteal phase. Pre-clinical research indicates that one mechanism for the pre-ovulatory decrease in eating is a central action of estrogens to increase the satiating potency of the gastrointestinal hormone cholecystokinin. Another mechanism involves a decrease in the preference for sweet foods during the follicular phase. Genetic defects in brain α-MSH–MC4R signalling lead to a syndrome of overeating and obesity that is particularly pronounced in women and in female animals. The syndrome appears around puberty in mice with genetic deletions of MC4R, suggesting a role of ovarian hormones. Emerging functional brain-imaging data indicate that fluctuations in ovarian hormones affect eating by influencing

striatal dopaminergic processing of flavour hedonics and lateral prefrontal cortex processing of cognitive inhibitory controls of eating. There is a dearth of research on the neuroendocrine control of eating after menopause. There is also comparatively little research on the effects of ovarian hormones on EE, although changes in ovarian-hormone levels during the menstrual cycle do affect resting EE.

Wider implications: Women's markedly greater obesity burden makes understanding the diverse effects of ovarian hormones on eating, EE and body adiposity urgent research challenges. A variety of research modalities can be used to investigate these effects in women, and most of the mechanisms reviewed are accessible in animal models. Therefore, human and translational research on the roles of ovarian hormones in women's obesity and its causes should be intensified to gain further mechanistic insights that may ultimately be translated into novel anti-obesity therapies and thereby improve women's health.

Introduction

That obesity is pandemic is well known (obesity is typically defined as body mass index [BMI, weight in kg / height in m^2]) ≥ 30). In contrast, that sex and gender are important variables in obesity is less well appreciated. In fact, worldwide, about twice as many women as men suffer from severe obesity (i.e., grade 2 and 3 obesity, BMI ≥ 35 and 40 kg/m^2, respectively) **(Figure 1)**. Although social factors, especially gender inequality, certainly contribute to male-female differences in obesity prevalence (Kautzky-Willer *et al.*, 2016), the consistent worldwide disparity in prevalence of severe obesity strongly suggests that biological factors, i.e., physiological sex differences, also contribute. In support of this, pre-clinical and clinical studies have revealed women-specific factors in the two physiological determinants of obesity, the level of energy intake, which is to say eating, and the level of energy expenditure (EE). Furthermore, this work indicates that ovarian hormones, in particular estrogens, influence both eating and EE in women. Finally, data also implicate ovarian hormones in the metabolic function of adipose tissue (AT). In light of these considerations, the goal of this review is to provide a critical update on the roles of ovarian hormones on the principle components of obesity, i.e., eating and EE, and on AT physiology.

Methods

Articles in English indexed in PubMed through January, 2016, were searched using the following keywords related to: (1) *reproductive hormones* [estrogen, estradiol, estrone, estriol, estrogen receptors 1 and 2 (ESR1 and ESR2 in humans, Esr1 and Esr2 in mice and rats; formerly known as ERα and ERβ, respectively), progesterone, progesterone receptor (2), androgen, androgen receptors*, weight regulation* [food intake, adipose tissue, adiposity, adipocyte, hunger, flavour hedonics, satiation, satiety, EE, physical activity, resting EE (REE), diet-induced EE, insulin, leptin, inflammation], ghrelin, cholecystokinin (CCK), glucagon-like peptide 1, peptide YY(3-36)], and (3) *central nervous system* (CNS) [neuropeptide Y, melanocortins, dopamine, serotonin, melanocortin receptor, agouti-related protein, nucleus of the solitary tract (NTS), striatum, putamen, nucleus accumbens, caudate

nucleus, frontal cortex, functional magnetic-resonance imaging (fMRI)]. Searches were of the form: body weight OR obesity AND (a *reproductive hormone* set element) AND (a *weight regulation* or *CNS* set element), where capital letters indicate Boolean connectors. We sought to identify emerging research foci with clinical translational potential rather than to provide a comprehensive review.

AT physiology

Measurement of body adiposity

Anthropomorphic adiposity measures, such as BMI, waist circumference (WC) and waist-hip ratio (WHR) are simple and inexpensive, but relatively imprecise measures of body adiposity. Errors are introduced by sex, age, ethnicity, and individual differences in body composition, such as muscle mass. For example, in one study, BMI misclassified the adiposity of one third of young adult female athletes (Ode *et al.*, 2007). Furthermore, BMI systematically over-estimates the adiposity of shorter people and under-estimates the adiposity of taller people. Both BMI and WC are better predictors of total-visceral AT (defined below) than WHR (Kamel *et al.*, 2000; Koren *et al.*, 2013; Pouliot *et al.*, 1994). In women, WC and WHR predicts cardiovascular disease better than BMI (Goh *et al.*, 2014). With respect to clinical practice, however, an expert panel (Klein *et al.*, 2007) concluded that additional anthropomorphic measures are unlikely to affect clinical management if BMI and standard cardiometabolic risk factors are considered (Kiernan and Winkleby, 2000).

Numerous other methods more accurately detect whole-body adiposity. Some, including, air displacement plethysmography and hydrostatic weighing (Fields *et al.*, 2015; Moon *et al.*, 2011; Silver *et al.*, 2010), are limited in their ability to measure regional AT differences. Dual-energy X-ray absorptiometry (DEXA) can detect regional fat and bone mineral density and with the aid of a special algorithm can distinguish intra-abdominal and subcutaneous fat (Kaul *et al.*, 2012), but it does not measure AT volume or distinguish water and other lean-tissue mass (Santen *et al.*, 2010). MRI and computed tomography (CT) are the best

168 available methods to measure AT volume and regional distribution *in vivo*. Whole-body
169 imaging (i.e., axial images every few cm) is most accurate. Single-level cross-sectional
170 images are more common, but which abdominal level best estimates central subcutaneous
171 and total-visceral AT is controversial (Kuk *et al.*, 2006; Shen *et al.*, 2012).
172
173 Histological or plasma assays may soon provide suitably accurate and clinically practical
174 measures of specific AT depots. For example, Lê et al. (Lê *et al.*, 2011) found that the
175 degree of macrophage infiltration in subcutaneous AT biopsies predicted total-visceral AT
176 volume, intrahepatic lipid content and several plasma markers of cardiometabolic-disease
177 risk. Therefore such methods may provide a safe and cost effective way to measure AT
178 compartments relevant for health in the future.
179

180 **General aspects of AT**

181 Energy is stored for long periods as intracellular droplets of triacylglycerol within adipocytes,
182 which are mostly organized in discrete AT depots (Rosen and Spiegelman, 2014).
183 Preadipocytes are pluripotent cells that can differentiate into white or brown adipocytes,
184 macrophages, muscle and bone progenitors (Tchkonia *et al.*, 2013). The differentiation of
185 adipocytes from preadipocytes is controlled by insulin-like growth factor, glucocorticoids, and
186 other growth factors and hormones (Cristancho and Lazar, 2011; Tang and Lane, 2012).
187 Although the roles of gonadal hormones in this process remain obscure, that estrogens play
188 an important role is indicated by the effect of estrogenic endocrine disruptors such as
189 bisphenol to disrupt normal pre-adipocyte differentiation in vitro and by their association with
190 obesity (Boucher *et al.*, 2014; Ohlstein *et al.*, 2014; Saal *et al.*, 2012).
191
192 The traditional view was that AT is a passive storage depot. AT energy storage is indeed
193 long term - the half-life of individual triacylglycerol molecules in the subcutaneous AT of
194 healthy humans is 1.6 years, orders of magnitude more than that of any other energy
195 metabolite (Arner *et al.*, 2011). Nevertheless, contemporary research clearly indicates, first,

196 that AT is a dynamic organ that contributes to metabolic homeostasis in multiple ways, and,
197 second, that in obesity, AT becomes dysfunctional and contributes to whole-body
198 pathophysiology and health risk. These pathophysiological processes are mediated both by
199 free fatty acids (FFA) and other metabolites released by AT and by signalling molecules
200 secreted by adipocytes, called adipokines, which have local (paracrine) and endocrine
201 signaling functions (Lee *et al.*, 2013; Tchkonia *et al.*, 2013). Additional signaling molecules
202 are secreted by AT endothelial cells and AT-resident immune cells.
203
204 A rough categorization of human AT includes five major depots (Shen *et al.*, 2003): (1)
205 Subcutaneous AT, which can be found from head to foot in obese individuals. Subcutaneous
206 AT includes superficial and deep sections separated by a fascial plane (Scarpa's fascia) in
207 the lower trunk and gluteal femoral areas. As described below, the different components of
208 subcutaneous AT are separately regulated. (2) Visceral or intraperitoneal AT, which includes
209 the omental (attached to the stomach), mesenteric (attached to the small intestine) and
210 epiploic (attached to the large intestine) depots. These depots contain numerous lymph
211 nodes and are especially prone to infiltration by macrophages during hypertrophy
212 (Gabrielsson *et al.*, 2003; Lee *et al.*, 2013; Tchkonia *et al.*, 2013). In addition, mesenteric AT
213 is exposed to absorbed lipids as they drain through the lymphatics. Finally, the vasculature of
214 visceral AT drains into the hepatic-portal vein, exposing the liver to increased levels of the
215 FFA, adipokines and immune mediators that it releases. (3) Retroperitoneal and pelvic AT
216 are separate depots, but are often categorized together with visceral AT because they
217 cannot be easily distinguished with imaging; we refer to this sum as "total-visceral AT". (4)
218 Intra- and extra-pericardial AT. (5) Intramuscular AT, which lies between the muscle
219 fascicles. Subcutaneous and visceral AT have received the most research and are the focus
220 of this review. Visceral fat is associated with impaired health while other AT compartments
221 contribute to a lower degree or may even have a protective effect (Després and Lemieux,
222 2006).
223

Vague (1947) first noted that, compared with men, women tend to have relatively more gluteofemoral AT and relatively less centrally located AT, i.e., abdominal subcutaneous and total-visceral AT. More recent studies confirmed this notion and indicate that these effects are evident across a wide range of BMI (Gallagher *et al.*, 2005). Nevertheless, there is substantial individual variation in obesity habitus. Indeed, some obese women have male-typical, central AT distribution (Karpe and Pinnick, 2015).

Female-typical adiposity

Puberty and young adulthhood

The typical female pattern of regional AT distribution emerges during puberty (Shen *et al.*, 2009; Taylor *et al.*, 2010)**.** In addition, healthy-weight females' greater absolute AT mass becomes obvious only after puberty (healthy weight is 18.5 – 24.9 kg/m^2). As a result, a normative young adult woman in the USA (height 1.6 m, BMI 22.5 kg/m^2) has ~18 kg body fat (~30% body weight), of which only ~5% is total visceral AT (Camhi *et al.*, 2011; Gallagher *et al.*, 1996; Shen *et al.*, 2009), whereas a normative male (height 1.8 m) has ~12 kg body fat (~15% body weight), of which ~11% is total visceral AT.

Female-typical AT results from differences among the AT depots in the balance of uptake and release of FFA (Santosa and Jensen, 2015). FFA uptake and triacylglyceride synthesis are greater in women's glutoefemoral than abdominal subcutaneous AT, and lipolysis rates are lower, thus selectively increasing the relative size of the gluteofemoral depot. These processes are controlled by complex interactions of genes and ovarian homones that are only beginning to be understood, for example with recent studies of differential AT gene expression (Fried *et al.*, 2015; Friedl *et al.*, 2015; Gesta *et al.*, 2006; Karpe and Pinnick, 2015). One study (Karastergiou *et al.*, 2013) found that of 284 genes that were differentially expressed in gluteofemoral compared with abdominal subcutaneous AT in overweight (mean BMI, 27 kg/m^2) adults, 159 were differentially expressed only in women. Furthermore, many of the genes were homeobox-family (*HOX*) genes, which are involved in cell differentiation.

252 Thus, a parsimonious hypothesis is that increased levels of estrogens or other reproductive
253 hormones during puberty differentially activate *HOX* and other genes to determine regional
254 AT distribution and physiology.
255
256 Mouse models provide further evidence that abdominal and gluteofemoral subcutaneous
257 adipocytes differentiate in a sex-dependent, cell-autonomous fashion (Fried *et al.*, 2015). For
258 example, estrogen receptor 1 (Esr1; formerly known as estrogen receptor-α) was necessary
259 for establishing the identity of mouse white-adipocyte progenitor cells (Lapid *et al.*, 2014),
260 and female transgenic mice lacking *Esr1* selectively in adipocytes became obese due to
261 expansion of gonadal AT, whereas additional knock out of *Esr2* (formerly estrogen receptor-
262 β) had no effect (Davis *et al.*, 2013). Although this result cannot be translated simply to
263 humans because humans do not have gonadal AT depots, the similar gene-expression
264 patterns of mouse gonadal AT and human omental AT (Gesta *et al.*, 2006) encourages the
265 view that estrogen-ESR1 signalling contributes similarly to the development of human
266 visceral AT. Finally, when the testes-determining *Sry* gene was transplanted from the Y
267 chromosome to an autosome in order to yield XX or XY mice with either male or female
268 gonads, XX mice had twice as much AT as XY mice independent of gonadal status,
269 indicating an important contribution of sex-linked genes to the sex difference in total body fat
270 (Chen *et al.*, 2012). Ongoing research is translating these kinds of data into human AT
271 physiology (Karastergiou *et al.*, 2013).
272
273 The search for genes mediating the high heritability of human obesity and regional AT
274 distribution has not yet been successful. The failure of most studies to take into account the
275 age of onset of obesity, in particular pubertal development, may contribute to this lack of
276 success. A recent large (n=224,459) genome-wide association study identified 49 single-
277 nucleotide DNA polymorphisms (SNP) related to WHR phenotypes, with 19 expressed more
278 in women (Shungin *et al.*, 2015). Overall, most SNP were in or near genes expressed by
279 adipocytes or related to insulin resisitance, suggesting that their analysis might lead to better

understanding of regional fat distribution and related pathophysiology. None was apparently related to *ESR1*, *ESR2*, androgen receptor or synthesis of estrogens or androgens, which might be expected to be especially important in the development of obesity during puberty. Interestingly, however, SNP associated with fat distribution had little overlap with those found in a similar analysis to be associated with BMI, which were predominately expressed in the brain (Locke *et al.*, 2015). This suggests that different biological processes underlie the accumulation and distribution of excess body fat (Fu *et al.*, 2015; Lee and Mattson, 2014). Moreover, epigenetic regulatory mechanisms, which are not revealed in SNP analyses, are also involved in the development of obesity (Dalgaard *et al.*, 2016).

Other methods have revealed some genes apparently involved in the estrogenic regulation of total adiposity. A study of SNP rs7757956 in intron 4 of *ESR1* indicated that an activational effect of estrogen signalling via ESR1 influences the development of obesity in pubertal girls (Tobias *et al.*, 2007). Girls, but not boys, on average 12 year-old, who were in Tanner stages 3-5 and bore a TT genotype at rs7757956 had 9% more body fat, as measured by DEXA, than TA- or AA-genotype girls. They also had 18% more height-adjusted body fat than TT-genotype girls in Tanner stages 1-2. As the TT genotype is common (75%), this may be an important contributor to female obesity. The influence of this SNP at later ages remains to be investigated.

Studies of hormonal contraception fail to reveal significant effects on body weight, Gallo et al. (2014) screened 734 English-language reports of effects of combination oral hormonal contraceptives or combination skin patches on body weight in healthy reproductive-age women and found 49 that met their quality criteria (inclusion of at least three cycles, inclusion of effect means and variabilities, etc.). These failed to show any consistent effect of combination contracptive use or its discontinuation on body weight, although the amount and quality of data were not judged to be of the highest quality. For example, only four studies included placebo-treated or no-intervention groups. A similar review of the effects of

progestin-only contraceptives on body weight identified only 15 studies, most of moderate to low quality (Lopez *et al.*, 2013). Twelve of these failed to detect weight changes, but in three there were weight gains of about 2 kg/y. Percent body AT was also increased in two studies in which body composition was measured. Thus, progestin-only contraception may slightly increase body weight and adipoisty, but available evidence does not establish this unambiguously.

Gonadotropin-releasing hormone (GnRH) agonists are often used to treat early or precocious puberty. Studies of the effect of GnRH-agonist treatment on weight gain are mixed, with some studies suggesting a small increase (Aguiar *et al.*, 2006; Wolters *et al.*, 2012), some a decrease (van der Sluis *et al.*, 2002), and others no effect (Głab *et al.*, 2009; Ko *et al.*, 2011). Interestingly, weight increase seems to occur only in girls who are healthy when initiating treatment, but not in girls who are overweight (Wolters *et al.*, 2012). GnRH agonists are also used in the treatment of endometriosis, but this is rarely done for more than six months in adult women due to deleterious effects on bone metabolism. Unfortunately, to our knowledge none of the studies investigating the use of GnRH agonists in women with endometriosis has described effects on body weight.

Menopause and hormone therapy (HT)

Aging *per se* increases adiposity, which complicates the estimation of the effects of menopause. Age and menopause are best segregated with multiple regression or similar statistical analyses, and therefore we consider only such studies. **Table 1** shows data from five such cross-sectional studies, four in which DEXA was used to estimate whole-body lean and fat masses (Ley *et al.*, 1992; Panotopoulos *et al.*, 1996; Svendsen *et al.*, 1995; Trémollieres *et al.*, 1996) and one in which whole-body MRI was used (Phillips *et al.*, 2008). Strikingly, these studies indicate that in both healthy-weight and mildly obese women, menopause increases body fat by ~5% of body weight and decreases fat-free body mass by a slightly smaller amount. These opposing changes explain why menopause has no marked

effect on body weight or BMI in most studies. The obvious clinical implication of these data is that women should be advised to lose several kg body fat during the menopausal transition in order to maintain cardiometabolic health.

Menopause appears to preferentially increase total-visceral AT, although the magnitude of the effect is uncertain. In two studies (Franklin *et al.*, 2009; Kanaley *et al.*, 2001) in which several axial MRI scans were made between the head of the femur and the kidneys in white US American women, both abdominal subcutaneous and total-visceral AT increased after menopause, with a slightly greater relative increase in total-visceral AT. In another MRI study (Phillips *et al.*, 2008), however, the relative increase in total-visceral AT was twice that of total AT. Several studies using DEXA confimed a correlation between postmenopausal status and increased total-visceral AT (Gambacciani *et al.*, 1999; Lovejoy *et al.*, 2008; Svendsen *et al.*, 1995; Trémollieres *et al.*, 1996). Even in non-obese women significant increases in total-visceral fat (Abdulnour *et al.*, 2012) and percent body lipid (Ho *et al.*, 2010) occurred during the menopausal transition. Moreover, in BMI matched (~25 kg/m^2) pre- and postmenopausal women, percent visceral AT was significantly lower in the premenopausal group, whereas no association of age and total-visceral AT was detected (Kanaley *et al.*, 2001).

We are not aware of imaging studies on the effects of surgical menopause by ovariectomy, on AT. Although results have to be interpreted with caution due to methodological limitations, such as lack of control for the indications for surgery or for hysterectomy vs. ovariectomy, available data support an association between surgical menopause and increased weight gain (Matthews *et al.*, 2001; Sowers *et al.*, 1996; Tom *et al.*, 2012), in line with the importance of ovarian hormones for obesity.

In younger post-menopausal women (age 50-59 y), estrogenic HT reduces fat mass, improves bone-mineral density, appears to preserve fat-free mass (FFM), reduces the risk of

type-2 diabetes mellitus, retards atherosclerosis, and reduces all-cause mortality (Manson and Kaunitz, 2016; Manson *et al.*, 2013; Santen *et al.*, 2010). At least in the case of atherosclerosis, benefits occur only if estrogenic HT is begun within less than ~6 y of menopause (Hodis *et al.*, 2016). In addition, estradiol treatment, but not progestin or testosterone treatment, lowered plasma very low-density lipoptrotein-triglyceride concentration ~30% in healthy postmenopausal women by increasing their plasma clearance (Smith *et al.*, 2014).

Santen and colleagues reviewed 13 placebo-controlled DEXA or CT studies studies in which unopposed estrogen HT or estrogen plus progestin HT reduced body fat. HT with progestins alone increased adiposity (Clark *et al.*, 2005; Dal'Ava *et al.*, 2014) indicating that the effects of HT on adiposity loss are purely estrogenic. Santen et al. (Santen *et al.*, 2010) also reviewed eight studies in which estrogenic HT reduced the tendency of postmenopausal women to develop more central obesity, versus two in which this was not the case, consistent with the data reviewed above indicating that estrogens contribute to the determination of regional adiposity distribution.

That estrogen levels are higher in non-obese than obese premenopausal women also supports a role of estrogens in restraining AT. Age-corrected early-follicular estradiol levels were 40 pg/mL in healthy-weight women vs. 33 pg/mL in obese women, with no overlap in 95% confidence intervals (95% CI) (Freeman *et al.*, 2010). In contrast, after menopause estradiol levels were lower overall, although higher in obese than non-obese women (21 vs. 12 pg/mL, no overlap in 95% CI). After menopause, estradiol originates mainly in the AT and appears to have no endocrine function.

It is important to emphasize that as a result of the opposite effects of HT on adiposity and FFM, HT leads to little or no change in total body weight. According to a Cochrane meta-analysis (Norman *et al.*, 2000) unopposed estrogen treatment had no significant effect on total weight (9 randomized controlled trials [RCT], mean difference vs. no HT, 0.0 kg, 95% CI

-0.6 - 0.7 kg) or BMI (2 RCT, mean difference -0.1 kg, 95% CI -0.4 - 0.1 kg); similarly, estrogen plus progestin treatment had no significant effect on weight (10 RCT, mean difference, 0.0 kg, 95% CI -0.4 - 0.5 kg) or BMI (10 RCT, mean difference -0.1 kg, CI -0.3 - 0.1 kg). Thus, women's fear that estrogenic HT leads to weight gain (Légaré *et al.*, 2000) is unfounded. Rather, the likelihood of benificial changes in body composition and metabolic health with estrogenic HT should be considered by women deciding on postmenopausal HT.

Obesity pathophysiology

Simple Obesity

Obesity causes progressive cardiometabolic dysfunction (Lumeng *et al.*, 2007; Mauvais-Jarvis *et al.*, 2013; Tchkonia *et al.*, 2013). Expanded AT depots release more FFA, which increase insulin secretion, decrease insulin sensitivity, and increase hepatic production of very low-density lipoproteins. In addition, hypertrophic adipocytes attract macrophages into the AT, which induces a sterile inflammation-like state characterized by secretion of numerous proinflammatory cytokines and adipokines. Finally, AT vasculature often fails to expand sufficiently in obesity, leading to local hypoxia that exacerbates the inflammatory state (Pasarica *et al.*, 2009; Sun *et al.*, 2013).

These processes are influenced importantly by ovarian hormones. For example, in rats, ovariectomy increases immune-cell infilatration into the AT and increases insulin resistance even if adiposity is controlled (Rogers *et al.*, 2009; Vieira Potter *et al.*, 2012). Increases in circulating adipokines and immune factors in postmenopausal women suggest similar effects contribute to increased risk of cardiometabolic diease in these women (Pfeilschifter *et al.*, 2002; Polotsky and Polotsky, 2010). Conversely, in younger women, HT reduces or delays these pathological processes (Manson and Kaunitz, 2016; Manson *et al.*, 2013; Santen *et al.*, 2010). Thus, studies of the roles of estrogens is an emerging theme in obesity-related cardiometabolic disease (Blenck *et al.*, 2016; DeClercq *et al.*, 2008; Monteiro *et al.*, 2014).

An additional potential mechanism through which estrogens improve AT function is related to the "browning" of white adipocytes (Palmer and Clegg, 2015), i.e., increased expression of uncoupling protein-1 (UCP-1), which generates heat without synthesizing ATP, thus increasing EE, and reduces cardiometabolic risk (Rosen and Spiegelman, 2014). Estrogens may induce browning in two ways. First, estrogens act in the heart to increase the secretion of cardiac natriuretic peptides (Jankowski *et al.*, 2001; Wang *et al.*, 2002), which in turn act in the AT to increase browning (Collins, 2014). Second, estrogens may increase hypothalamic expression of brain-derived neurotrophic factor, which increases sympathetic outflow to the AT and increases browning (Cao *et al.*, 2011; Palmer and Clegg, 2015).

Different AT depots are differentially predisposed to obesity-related pathophysiology (Fried *et al.*, 2015; Karpe and Pinnick, 2015; Lee *et al.*, 2013; Tchkonia *et al.*, 2013) **(Figure 2)**. Centrally located AT, especially visceral AT, brings the greatest health risk (Després and Lemieux, 2006; Pischon *et al.*, 2008; Wang *et al.*, 2005). A variety of data indicate that this is related to the direct delivery of FFA and proinflammatory immune mediators to the liver (Bergman *et al.*, 2006; Item and Konrad, 2012; Rytka *et al.*, 2011). Indeed, omental AT resection added further metabolic benefits to Roux-en-Y gastric bypass surgery (Dillard *et al.*, 2013). Mesenteric AT appears to be even more toxic, as in comparison to subcutaneous or omental AT, it is more densely innervated by sympathetic efferents, expresses more glucocorticoid receptors, and is more prone to macrophage migration (Tchkonia *et al.*, 2013). Abdominal subcutaneous AT also has adverse metabolic characteristics (Tchkonia *et al.*, 2013), especially deep subcutaneous AT (Koster *et al.*, 2010; Smith *et al.*, 2001).

In contrast to all other AT depots, gluteofemoral superficial subcutaneous AT actually reduces cardiometabolic-disease risk (Koster *et al.*, 2010; Lee *et al.*, 2013; Snijder *et al.*, 2004; Yusuf *et al.*, 2005). Indeed, women with marked gluteofemoral obesity often remain metabolically healthy (Karpe and Pinnick, 2015). Many factors appear to contribute to the development of larger gluteofemoral subcutaneous AT depots in women and to this depot's

448 protective nature (Karpe and Pinnick, 2015; Lee *et al.*, 2013; Santosa *et al.*, 2008; Tchkonia
449 *et al.*, 2013). Gluteofemoral subcutaneous AT releases more of the insulin-sensitizing
450 adipokine palmitoleate than abdominal subcutaneous AT (Pinnick *et al.*, 2012). Adipocytes in
451 gluteofemoral subcutaneous AT also have greater lipoprotein-lipase activity in women than
452 men, indicating that they more effectively clear triacylglyceride after meals (Votruba and
453 Jensen, 2007). Moreover, uptake of plasma FFA, lipogenesis and triacylglycerol re-
454 esterification are greater in women's gluteofemoral subcutaneous AT than in their abdominal
455 subcutaneous AT, whereas the opposite is true in men (Koutsari *et al.*, 2011; Søndergaard *et*
456 *al.*, 2012). Together, these characteristics of women's gluteofemoral subcutaneous AT
457 contribute to the greater size of this depot, the greater stability of stored triacylglycerol, and
458 the lower plasma FFA levels.
459
460 Another factor relevant to sex differences in AT function is the greater proliferative potential
461 of preadipocytes in subcutaneous vs. visceral AT. For example, Tchoukalova and colleagues
462 (Tchoukalova *et al.*, 2010) overfed healthy-weight men and women (mean BMI, 22.1 kg/m^2)
463 for eight weeks, leading to a gain of 3.8 kg fat mass and an increase in mean BMI to 23.6
464 kg/m^2. Strikingly, women displayed greater AT hyperplasia, so that their average adipocyte
465 size decreased with weight gain. This was most evident in the femoral fat, and was
466 associated with relatively greater expansion of gluteofemoral than central AT. In addition,
467 women with larger baseline abdominal subcutaneous adipocytes also displayed marked
468 hyperplasia in that depot. This suggests that as AT expands in obesity, the larger number of
469 gluteofemoral adipocytes in women permits them to store more triacylglycerol before
470 reaching dysfunctional degrees of hypertrophy (Tchkonia *et al.*, 2013). Unfortunately, the
471 specific effects of ovarian hormones on adipose-tissue cell biology have not yet been
472 intensively researched. This is a major challenge facing women's health research.
473
474

Polycsytic Ovary Syndrome (PCOS)

PCOS is characterized by hyperandrogenism, chronic anovulation and polycystic ovaries (Dumesic *et al.*, 2015; McCartney and Marshall, 2016). One of the primary pathological changes thought to lead to PCOS is increased ovarian androgen secretion. Indeed, increased androgen production occurs even in theca cells cultured from women with PCOS (Nelson *et al.*, 1999). This pathology may be caused in some women by polymorphisms of *DENND1A*, which encodes a protein affecting the placement of cell-surface receptors (McAllister *et al.*, 2014).

Although the prevalence of PCOS is similar in healthy-weight, overweight and obese women (Yildiz *et al.*, 2008), about 40-50% of PCOS patients are obese (Carmina *et al.*, 2009; Teede *et al.*, 2010). Some studies suggest that PCOS is associated with greater abdominal obesity (e.g., (Carmina *et al.*, 2007), but this is controversial (Barber *et al.*, 2008). Although obesity pathophysiology related to PCOS is poorly understood, several results support key roles of increased estrogen and androgen secretion. Androgens can lead to dyslipidemia indirectly by exacerbating insulin resistance, leading to altered lipid metabolism and body composition, and directly, through effects in the AT (Diamanti-Kandarakis, 2007). Whether AT dysfunction is primary or secondary to hyperandrogenism or other abnormalities in PCOS, however, remains unknown (Villa and Pratley, 2011). Women with PCOS have lower lipoprotein lipase (LPL) expression in subcutaneous AT than healthy women (Mannerås-Holm *et al.*, 2014). Both androgens and estrogens inhibit AT LPL activity (Blouin *et al.*, 2010; Pedersen *et al.*, 2004), and even after controlling for BMI, expression of LPL in the subcutaneous AT correlated negatively with plasma estradiol (Mannerås-Holm *et al.*, 2014). Excessive visceral fat distribution (Diamanti-Kandarakis, 2007; Escobar-Morreale and San Millán, 2007) and disturbed adipokine release seems to influence PCOS development (Torres-Leal *et al.*, 2010; Villa and Pratley, 2011). For example, in women with PCOS, leptin expression was reduced in the subcutaneous AT, adiponectin expression was reduced in both subcutaneous and omental AT, and adiponectin receptor-2 expression was reduced in subcutaneous AT

(Carmina *et al.*, 2008; Mannerås-Holm *et al.*, 2014). These and other adipokines may modulate the hypothalamic-pituitary-gonadal axis through receptors in pituitary FSH, LH and TSH cells (Psilopanagioti *et al.*, 2009; Sone *et al.*, 2001; Taheri *et al.*, 2002) so as to increase ovarian hormone secretion in patients with PCOS (Olszanecka-Glinianowicz *et al.*, 2011; 2013). Additionally, some adipokines may directly influence ovarian steroidogenesis (Tersigni *et al.*, 2011). Consistent with a link between decreased adipokines and increased ovarian hormone secretion, plasma estradiol levels were negatively correlated with adiponectin receptor-1 in the subcutaneous AT of women with PCOS independent of BMI; testosterone levels, however, were not significantly correlated with adiponectin receptor-1 (Mannerås-Holm *et al.*, 2014). Interestingly, although AT inflammation was not different in women with PCOS and BMI-matched control women **(**Lindholm *et al.*, 2011), adiponectin release in response to the proinflammatory cytokine tumour necrosis factor-α was decreased in adipocyte obtained from overweight or obese women with PCOS (Chazenbalk *et al.*, 2010).

EATING

General aspects of the control of eating

The intake of metabolic energy occurs mainly in the form of meals (including snacks). Meals and the surrounding affective and cognitive processes are the products of a widely distributed information-processing network in the brain, described below, that produces conscious and unconscious responses that underlie planning to obtain food, motivational urges to eat, planning to obtain food, eating *per se*, the pleasurable, or hedonic, aspects of eating, satiation, and the effects of nutrient repletion on learning.

The primary internal stimuli controlling eating include the subjective value assigned to food and neural and endocrine feedbacks from the gastrointestinal (GI) tract, from AT, and from metabolic processes. “Food value” in this context refers to reinforcement, i.e., the ability of food stimuli to support learning, to generate approach behaviour, and to elicit emotional

responses, including flavour hedonics (Schultz, 2015). Beyond these, there are several secondary or modulatory internal factors, ranging from circadian rhythm to psychological factors and motivators such as stress, emotional state, cognitive control, etc. As reviewed below, reproductive hormones importantly modulate these physiological controls of eating (Asarian and Geary, 2013; López and Tena-Sempere, 2015; Mauvais-Jarvis *et al.*, 2013). External stimuli, in particular stimuli with learned cognitive and affective meanings, also play important modulatory roles in eating (French *et al.*, 2012; Higgs *et al.*, 2012). There is a dearth of research on the influence of reproductive hormones on these controls of eating. This is unfortunate because, for example, estrogens and their lack after menopause can influence affective (Joffe *et al.*, 2011; Schmidt *et al.*, 2015) and cognitive (Hara *et al.*, 2015) functions in women.

Roles of ovarian hormones

The best-established effect of ovarian hormones on eating is the progressive decrease in eating during the follicular phase of the menstrual cycle. In healthy-weight cycling women, food intake decreases ~200-300 kcal/d from the luteal maximum to the peri-ovulatory minimum **(Figure 3)**, an amount relevant to body-weight regulation (Asarian and Geary, 2013; Hall *et al.*, 2011). Available data indicate that eating does not decrease during anovulatory cycles (Barr *et al.*, 1995; Rock *et al.*, 1996), that the decrease in ovulatory cycles is due to decreased meal size rather than decreased meal frequency (Brennan *et al.*, 2009; Pohle-Krauza *et al.*, 2008) and related to a decrease in the intake of sweet foods (Bowen and Grunberg, 1990; Fong and Kretsch, 1993), Old-world monkeys and apes (Parvorder *Catarrhini*), which have ovarian cycles similar to those of women (Zeleznic and Pohl, 2006), as well as mice, rats and many other species display comparable cyclic decreases in meal size and food intake. Loss of estrogens after ovariectomy increases meal size, food intake and body weight in old-world monkeys, rats and mice (Asarian and Geary, 2013; Bellino and Wise, 2003; Sullivan *et al.*, 2005), suggesting that increased eating contributes to the increase in AT after menopause in women, but whether this is so is unknown.

559 Experiments in rats and mice indicate that estrogens signalling via Esr1 receptors mediate
560 cyclic change in eating in those species, which appear to correspond to the decrease in
561 eating during the human follicular and peri-ovulatory phases (Asarian and Geary, 2013). Rats
562 and mice do not have luteal phases, however, and the control of eating in this phase of the
563 menstrual cycle is less well understood. Although it is reasonable to hypothesize that
564 progestins oppose the inhibitory effects of estrogens during the luteal phase, data fail to
565 support this. Physiological doses of estradiol inhibited eating in ovariectomizued rhesus
566 macaques, and this was not affected by progesterone treatment (Czaja, 1978). Similarly,
567 estrogen together with escalating progestin doses failed to affect eating women (Eck *et al.*,
568 1997), although the experiment was limited because the participants were cycling, so that the
569 treatment effects may have been obscured by the effects of endogenous hormones, and
570 because diet records, rather than measure of actual eating, were used. In addition, depot
571 medroxyprogesterone failed to affect food intake in an adequately powered, prospective,
572 placebo-controlled study in cycling women (Pelkman *et al.*, 2001).
573
574 Binge eating, referring to eating an abnormally large amount of food on a single occasion
575 with a feeling of loss of control over eating, is a dysregulated form of eating especially
576 prevalent in girls and women (Hilbert *et al.*, 2012; Reichborn-Kjennerud *et al.*, 2003). Binge
577 eating is prodromal to bulimia nervosa, binge-eating disorder, and obesity. It is also highly
578 heritable (Davis, 2015). Female rats are much more prone than male rats to develop binge-
579 like eating (Klump *et al.*, 2013). Related to binge eating is emotional eating, i.e., eating in
580 response to negative emotions, and this is also more prevalent in girls and women.
581
582 Binge eating develops most often during puberty, in association with higher estrogen levels
583 (Klump *et al.*, 2010). In addition, binge and emotional eating vary through the menstrual
584 cycle, with lower rates in the late-luteal through the peri-ovulatory phases and higher rates
585 during the mid-luteal phase (Culbert *et al.*, 2016). A time-series analysis of binge tendencies
586 and ovarian hormone levels through the cycle suggested that estrogens inhibit emotional and

587 binge eating and progestins oppose this effect of estrogens, i.e., indirectly stimulate
588 emotional and binge eating (Klump *et al.*, 2014). This is the strongest indication that
589 progestins are clinically important in dysregulated eating in human females. Estradiol, but not
590 progesterone, reduced amount eaten during binge-like episodes in rats (Yu *et al.*, 2011), but
591 whether this is a useful model of binge size or frequency in women is not known.
592
593 *Peripheral mechanisms*
594 Taste. Although the perception of sweet and creaminess differs in men and women
595 (Bartoshuk *et al.*, 1994; Hayes and Duffy, 2008) and women's intake of sweet food increases
596 during the luteal phase (Bowen and Grunberg, 1990) and during pregnancy (Belzer *et al.*,
597 2010), the roles of ovarian hormones in these phenomena have not been carefully
598 investigated (Asarian and Geary, 2013).
599
600 GI signals. A variety of GI neural and endocrine signals are candidate meal-control
601 mechanisms (Asarian and Geary, 2013; Camilleri, 2015). Unfortunately, research on their
602 operation in women remains sparse. Ghrelin, a hormone secreted by the stomach, stimulates
603 meal initiation and increases meal size. In rats, there was an estradiol-dependent increase in
604 ghrelin's eating-stimulatory effect during the first two days of the four-day ovarian cycle
605 (ovulation occurs on the last night), and ghrelin levels increased after ovariectomy in parallel
606 to the increase in eating (Clegg *et al.*, 2007). The small-intestinal hormone cholecystokinin
607 (CCK) reduces meal size by hastening meal termination, i.e., by producing satiation. CCK is
608 the only endocrine meal-control signal that can be considered to have a proven normal or
609 "physiological" role in humans. That is, intravenous infusion of CCK in amounts that mimic
610 prandial changes in plasma levels is sufficient to reduce meal size, CCK-receptor
611 antagonists reduce the satiating potency of intraduodenal fat infusions, and CCK-receptor
612 antagonists administered alone increase meal size (Geary and Moran, 2016). In rats,
613 estrogens act via Esr1 in the hindbrain to increase CCK's satiating action (see below).
614 Unfortunately, whether estrogens affect CCK satiation in women is unknown. The intestinal

615 hormones glucagon-like peptide-1 (GLP-1) and peptide YY(3-36) are also candidate eating-
616 inhibitory signals, and estradiol increases GLP-1 satiating action in ovariectomized rats
617 (Asarian and Geary, 2013).
618
619 Leptin. Endocrine signals related to AT mass, notably leptin and insulin, contribute to the
620 control of eating (Le Foll *et al.*, 2014; Levin *et al.*, 2011). Leptin is secreted by white
621 adipocytes, and basal (fasting) plasma leptin levels are highly correlated with AT mass.
622 Interestingly, for a given level of fat mass, leptin levels are higher in women than men, and
623 this difference decreases after menopause. Estrogen levels and differences in intra-
624 abdominal and subcutaneous AT distribution contribute to these effects (Rosenbaum and
625 Leibel, 1999; Rosenbaum *et al.*, 2001). Originally hypothesized to be the crucial link between
626 body adiposity and the controls of eating and EE, leptin is now considered to defend only
627 against reductions in body weight, not against weight increases (Ravussin *et al.*, 2014).
628 Whether estrogens interact with leptin to control eating is controversial. In ovariectomized
629 rats, estradiol increased the eating-inhibitory potency of acute leptin injections (Clegg *et al.*,
630 2003), but not that of chronic leptin treatment (Chen and Heiman, 2001). Furthermore, food
631 intake was not correlated to plasma leptin levels in cycling women (Paolisso *et al.*, 1999).
632 None of these studies, however, was done in the weight-reduced state when leptin's
633 contribution to eating is greatest.
634
635 The brain mechanisms mediating potential interactive effects of leptin and estrogens on
636 eating are also uncertain. In mice and rats, Esr1 is expressed in about 10% of neurons that
637 express the signaling leptin receptor (Leprb) in the arcuate nucleus of the hypothalamus
638 (ARC), the caudal medial nucleus of the solitary tract (cmNTS) in the brainstem, and several
639 other areas thought to mediate the control of eating (Asarian, unpublished data; (Kim *et al.*,
640 2016)). Esr1/Leprb co-expression is much higher, ~80%, in the preoptic area (Kim *et al.*,
641 2016), one of the brain sites containing the GnRH neurons that control FSH and LH secretion
642 (Herbison, 2006). Kim and colleagues (Kim *et al.*, 2016) reported that although food intake

643 was increased in transgenic mice lacking Esr1 in Leprb neurons globally, estradiol treatment
644 did not activate Leprb neurons in the ARC of ovariectomized mice, suggesting that estrogens
645 and leptin do not affect ARC Esr1/Leprb neurons to inhibit eating. In contrast, Asarian
646 (unpublished data) found that knockdown of Leprb neurons in the mNTS with RNA-
647 interference increased eating and completely prevented estradiol from inhibiting food intake
648 in ovariectomized rats, suggestng an Esr1/Leprb interaction in the mNTS is necessary for the
649 normal control of eating.
650
651 Insulin. Basal plasma levels of insulin also correlate with body fat mass, and insulin may act
652 in the brain to control eating and EE. Estrogens appear to regulate the effects of insulin on
653 eating. Central administration of insulin inhibited eating more ovariectomized than in intact
654 rats, and this was reversed by central estradiol administration (Clegg *et al.*, 2006). These
655 effects do not occur in peripubertal rats (Keen-Rhinehart *et al.*, 2009), further suggesting an
656 activational role of estradiol. Interestingly, female, but not male, transgenic mice with brain-
657 specific null mutations of the insulin receptor are hyperphagic, which in females was related
658 to profound reductions of LH and signs of defective ovarian follicle maturation, indicating a
659 role for neural insulin receptors in the normal function of the hypothalamic-pituitary-gonadal
660 axis (Brüning *et al.*, 2000).
661
662 Intra-nasal insulin delivery has been used to selectively stimulate brain insulin receptors in
663 humans. Similar to the rat studies, intra-nasal insulin before meals decreased eating more in
664 men than in reproductive-age women (Benedict *et al.*, 2008). In apparent contast to the
665 findings of Clegg and colleagues (Clegg *et al.*, 2006) in rats described above, premeal intra-
666 nasal insulin failed to inhibit eating in post-menopausal women (Krug *et al.*, 2010). In
667 contrast, intra-nasal insulin given after meals reduced subsequent intake of preferred snack
668 foods in young women taking high-estrogen contraceptives, suggesting that insulin increases
669 postprandial satiety in women (Hallschmid *et al.*, 2012). These data suggest that central
670 insulin-based pharmacotherapy might be an effective obesity treatment in women.

Central mechanisms

A widely distributed central neural network controls eating (Berthoud, 2002; Castro and Berridge, 2014; Farr *et al.*, 2016; Geary and Moran, 2016; Grill and Hayes, 2012; Schultz, 2015; Shin *et al.*, 2009; Val-Laillet *et al.*, 2015). Local circuits in the caudal brainstem integrate a variety of sensory inputs, including gustatory, vagal afferent, spinal visceral afferent, and many GI-hormone signals, and also produce the consummatory behaviors of eating. Animal studies indicate that the hypothalamus plays the leading role in homeostatic eating, i.e., eating stimulated by nutrient depletion. Additional cerebral regions involved in eating include primary and secondary gustatory regions (insula and orbitofrontal cortex) as well as regions involved in memory (hippocampus) and cognitive control (dorsolateral prefrontal cortex, inferior frontal cortex, and cingulate cortex). Neuropharmacological and molecular genetic studies in animals and fMRI studies in humans indicate that the striatum (which consists of the nucleus accumbens, caudate nucleus and putamen), the orbitofrontal cortex, the amygdala, and the midbrain dopamine neurons perform neural computation of the subjective value of food stimuli ("value" was defined above). Estrogens and other gonadal steroids diffuse freely through the blood-brain barrier (Pardridge *et al.*, 1980), act on cognate receptors in several of these areas, and through them affect eating-related neural information processing in these areas and in areas linked to them via neural projections (López and Tena-Sempere, 2015) **(Figure 4)**.

Studies in rats indicate that estrogen-Esr1 signalling in neurons in the cmNTS in the caudal brainstem controls the estrogenic inhibition of normal eating (Asarian and Geary, 2013). That is, knockdown of cmNTS Esr1 with RNA interference increased eating and body weight and completely blocked the usual eating-inhibitory effect of estradiol in ovariectomized rats. No other brain site has been similarly linked to the estrogenic control of eating (e.g., ARC data were discussed in the leptin sections) (Asarian and Geary, 2013). The network effects of cmNTS estrogen stimulation, of course, may involve the hypothalamus and other forebrain sites. For example, expression of the neurotransmitter agouti-related protein (AgRP) in

699 neurons in the ARC changes across the ovarian cycle in mice, and transgenic lesions of
700 AgRP neurons prevented the cyclic decrease in eating; these neurons do not express Esr1,
701 however, indicating that these effects are functionally downstream of estrogens' neural
702 actions (Olofsson *et al.*, 2009).
703
704 AgRP neurons appear to be selectively involved in the aversive, homeostatic hunger
705 produced by prolonged food deprivation, in contrast to the incentive-state like hunger that is
706 more operative in spontaneous eating (Betley *et al.*, 2015). AgRP neurons secrete the
707 neurotransmitters NPY and glutamate as well as AgRP, and these molecules appear to have
708 temporally distinct contributions to hunger (Krashes *et al.*, 2013). Unfortunately, the roles of
709 ovarian hormones in these effects have not yet been tested. It is important to note in this
710 regard that specific aspects of eating are likely to involve Esr in different sites. For example,
711 binge-like eating in mice apparently depends on estrogen-Esr1 signaling in serotoninergic
712 neurons in the dorsal raphe nuclei (Cao *et al.*, 2014). This is especially interesting because
713 women with bulimia nervosa had reduced serotonin-transporter binding in the dorsal raphe
714 both during active bulimia nervosa and after recovery (Pichika *et al.*, 2012).
715
716 Pro-opiomelanocortin neurons, which release the neurotransmitters α-melanocycte-
717 stimulating hormone and β-endorphin, also may be involved in the estrogenic inhibition of
718 eating. Brain α-melanocycte-stimulating hormone neurons signal mainly via melanocortin-3
719 receptors in the ARC and melanocortin-4 receptors (MC4R) in the paraventricular nucleus of
720 the hypothalamus (Biebermann *et al.*, 2012), and loss-of-function polymorphisms of human
721 *MC4R* lead to voracious appetite and obesity (Dempfle *et al.*, 2004; Stutzmann *et al.*, 2008;
722 Valette *et al.*, 2013). *MC4R* defects have a prevalence of □2-5% in obese Europeans,
723 making it one of the commonest of all genetic diseases (O'Rahilly and Farooqi, 2006; Tao,
724 2010). Importantly, weight gain is about twice as much in women as in men, □8-9 kg/m^2 vs
725 □4-5 kg/m^2. Mice with null mutations of this gene (Mc4r-/- mice) show a similar syndrome,
726 again with a marked sex difference that begins around puberty, suggestive of activational

effects of reproductive hormones (Huszar *et al.*, 1997). In contrast, obesity was already present in pre-pubertal boys and girls with either of two *MC4R* polymorphisms (Vogel *et al.*, 2011). Separate analyses of just one of these, SNP rs17782313, however, unveiled a pronounced sex difference. In women bearing this SNP, but not in men, there were increases in the eating traits disinhibition and emotional eating as well as differences in gray-matter volume in the eating-related areas including the right amygdala, right hippocampus, and medial orbitofrontal cortex (Horstmann *et al.*, 2013). The effects of estrogens on POMC neurons may be mediated by both Esr1 (Xu *et al.*, 2011) and the recently discovered Gq-coupled membrane estrogen receptor (Smith *et al.*, 2013). Whether estrogens act directly on POMC neurons or indirectly and the sites involved, however, is unknown.

Human functional neuroimaging studies converge with animal studies in identifying subcortical and cortical brain structures that are involved in the control of eating. Typically, these studies localize regions that respond differently to food and non-food stimuli, to hunger and satiety, and in obese and normal-weight women (Morris and Dolan, 2001; Salem and Dhillo, 2015; Schur *et al.*, 2009; Small and Prescott, 2005; Stoeckel *et al.*, 2008; Wang *et al.*, 2004). Both animal and human receptor expression studies suggest that reproductive hormones are in a position to affect the function of these regions. For example, in humans, ESR1 receptors are abundant in the hypothalamus, amygdala, hippocampus, nucleus accumbens and several cortical regions (Hara *et al.*, 2015). Importantly, this includes membrane estrogen receptors, which mediate rapid effects on neural activity, as well as classical nuclear estrogen receptors (Almey *et al.*, 2015). Furthermore, estrogens are required to maintain dopamine innervation of the striatum, and estrogen and/or progesterone replacement can rescue ovariectomy-induced reductions in caudate dopamine (Kritzer *et al.*, 2003). Progesterone receptors are also expressed in food-related regions beyond the hypothalamus, including the caudate (Zhu *et al.*, 2003), amygdala, hippocampus, and frontal cortex (Brinton *et al.*, 2008). Although the exact role of hormones in many of these regions is not entirely clear, the widespread distribution of their receptors in areas mediating hedonics,

motivation and cognition reinforces the notion of their involvement in non-reproductive neural functions, particularly in the control of normal and dysreguated eating.

There are sex-related structural differences in brain areas involved in processing food-related information (Ruigrok *et al.*, 2014); for example, women compared with men express relative increases in regional grey matter volume or density in frontal cortex, dorsal striatum and right insula, but relative reductions in ventral striatum, amygdala, hippocampus and left insula. Sex modulates the functional activation of these regions in a corresponding way. Obese women show different neural responses to pictures of high-energy food than lean women or obese men. For example, dorsal striatum activity to high-energy food pictures is particularly enhanced in obese women (Geliebter *et al.*, 2013; Rothemund *et al.*, 2007). Rodent research implicates the dorsal striatum in the development of inflexible, habitual control of eating (Furlong *et al.*, 2014). Accordingly, eating habits may be particularly inflexible in obsese women.

Changes in neural responses to food pictures through the menstrual cycle suggest a role of ovarian homones in processing food-related information. Accordingly, the reduced food intake in the peri-ovulatory phase of the menstrual cycle is reflected in changes in the responses of eating-related regions. Specifically, the ventral striatum shows enhanced activity to high versus low energy-food pictures during the peri-ovulatory compared with the luteal phase (Frank *et al.*, 2010), in line with the notion of enhanced dopaminergic reward activity during the peri-ovulatory phase (Dreher *et al.*, 2007; Frank *et al.*, 2010). In a separate group of subjects, these neural effects were mirrored by reduced appeal of high energy-food pictures during the peri-ovulatory phase compared with the luteal phase, with unchanged appeal of low energy-food pictures. Thus, the meal size-limiting effects of estrogens during the peri-ovulatory phase are mediated by increased ventral striatal responses to high-calorie food, reflecting increased reward sensitivity induced by higher levels of estrogens. Indeed, separate research showed a positive correlation between estradiol levels and amphetamine-

induced euphoria in women during the follicular, but not the luteal, phase, suggesting that estrogens make women more sensitive to (striatal) dopamine (Justice and de Wit, 1999). These findings converge with reports of reduced reward sensitivity and dopamine release in obesity and therefore conceptualize increased food intake as an attempt to compensate for reduced reward value of food (for review, see Val-Laillet *et al.*, 2015).

Moreover, neural responses to food pictures reflect interactions between prandial state and menstrual-cycle phase. Specifically, responses to food pictures in the lateral prefrontal cortex are enhanced in the fed compared with the hungry state during the late follicular (high-estrogen), but not the early follicular (low-estrogen), phase (Alonso-Alonso *et al.*, 2011). Thus, estrogens may act in the prefrontal cortex to facilitate cognitive control over appetite in the fed state, i.e., reduce the tendency to "eat in the absence of hunger," a trait associated with increased obesity risk (French *et al.*, 2012). In line with this notion, the lateral prefrontal cortex is less activated after meals in obese women than in lean or formerly obese women (Le *et al.*, 2007). Furthermore, stronger lateral prefrontal responses to food pictures predict reduced subsequent energy intake (Cornier *et al.*, 2010), and these responses are smaller in obese compared with healthy-weight individuals (Batterink *et al.*, 2010).

Although converging evidence from human neuroimaging studies identifies regions involved in mediating the influence of ovarian hormones on processing food-related stimuli, there is a dearth of studies that directly investigate the effects of sex and ovarian hormones on precisely defined components of neural processing related to eating. Addressing this gap would involve using real food rather than pictures and paradigms established in the fields of reinforcement learning, affective neuroscience, and decision neuroscience. For example, it would be interesting to directly test the effects of estrogens on the neural mechanisms underlying Pavlovian and goal-directed aspects of eating. One hypothesis would be that estrogens act in the striatum to make eating behavior flexible and goal-directed.

Energy Expenditure (EE)

General aspects of human EE

EE is energy lost in work or heat (urinary nitrogen and glucose losses can also contribute in pathological situations). Total EE includes REE, the postprandial increase in EE due to digestive and metabolic handling of ingesta (known as diet-induced thermogenesis (DIT) or the thermic effect of food), thermoregulatory responses, weight-regulatory EE responses, and physical-activity EE. REE is also known as resting or basal metabolic rate and is sometimes subdivided into sleeping and awake, resting components. In moderately active individuals in a thermoneutral environment, REE usually accounts for ~60-70% of total EE (Levine, 2004), DIT for ~10-15% (D'Alessio *et al.*, 1988; Reed and Hill, 1996) and physical activity for the rest. Physical-activity EE can be further subdivided into exercise or sports activities (including walking for exercise) and non-exercise-activity thermogenesis, which is the energetic cost of occupational physical activity and incidental daily activities, such as sitting, talking, standing, fidgeting, etc.

REE is strongly correlated with FFM (r^2 ~0.6-0.7), with no sex difference (Blundell *et al.*, 2010; Johnstone *et al.*, 2005). Individuals with lower REE/FFM values are at increased risk for weight gain (Ravussin *et al.*, 1988), suggesting that genetic differences in the cellular components of REE may contribute to individual differences in obesity risk (Konarzewski and Książek, 2013). About half of REE is due to membrane processes, mainly Na^+/K^+-ATPase and UCP-mediated mitochondrial proton leak (Hulbert and Else, 2005). A decline in UCP activity may explain the decrease in REE with aging (Saito, 2013; St-Onge and Gallagher, 2010) which, as reviewed below, complicates studies of menopausal effects on REE.

The much lower requirement for physical-activity EE in developed societies is thought to contribute to the obesity epidemic and to disease risk (Woolf *et al.*, 2008). Physical activity not only directly increases EE, but also increases REE (Gilliat-Wimberly *et al.*, 2001; Van Pelt *et al.*, 2001). Physical-activity EE can be expressed as metabolic-energy equivalents

(MET), the ratio of the rate of EE during the activity and a standard rate, which was originally based on EE while sitting quietly (ASHRAE, standard 55). Only a few physical laborers or athletes regularly exceed a daily average level of 2 MET (Levine, 2004). The recommended minimal level of physical activity for good health in the USA is 500 MET-min/wk (ODPHP, 2016). As moderate-intensity activity, such as walking at ~5 km/h, expends ~3.3 MET and vigourous-intensity activity, such as jogging at ~8 km/h, expends ~6 MET, this recommendation can be met by walking for ~150 min/wk or jogging for ~75 min/wk. Epidemiological data indicate that any level of physical activity reduces adult all-cause mortality risk and that exceeding the MET recommendation 2-fold or more reduces it by ~30-40% (Arem, Moore, *et al.*, 2015). Only 40% of US Americans, however, meet this recommendation.

Increased physical-activity EE improves cardiovascular fitness and reduces all-cause mortality independent of BMI (Barry *et al.*, 2014). Furthermore, higher levels of physical-activity EE predict success in maintaining diet-induced weight loss (Phelan *et al.*, 2006). Thus, women should be encouraged to increase physical-activity EE, especially after menopause and in societies in which they tend to be less active (Ford *et al.*, 1991; Livingstone *et al.*, 2001; Sadarangani *et al.*, 2014). The physiological mechanisms mediating these mortality effects are not known. Unfortunately, the substantial error in available methods for measuring habitual physical-activity EE (Arem, Keadle, *et al.*, 2015; Lim *et al.*, 2015) impedes research progress in this area.

Finally, alterations in total EE contribute to body-weight regulation (Dhurandhar *et al.*, 2015; Hall *et al.*, 2011; Leibel *et al.*, 1995). If body weight decreases, total EE decreases markedly more than predicted by the lower body mass, thus strongly resisting further weight loss. This adaptive reduction in EE is one reason weight loss is so difficult. For example, a reduction in habitual intake by 200 kcal/d will lead to 19 kg weight loss in 3 y, vs. a predicted weight loss of 78 kg if there were no adaptation in EE (Hall *et al.*, 2011). The underlying mechansims are not fully understood. Changes in the amount or efficiency of physical-activity EE (Leibel *et*

867 *al.*, 1995; Levine, 2004; Levine *et al.*, 1999) and in UCP-1 expression in brown-AT (Fromme
868 and Klingenspor, 2011; Morrison *et al.*, 2014) appear to contribute.
869
870 **Roles of ovarian hormones**
871 *REE*
872 REE per kg body mass is lower in women due to their higher percent AT, but REE per kg
873 FFM does not appear to differ between the sexes (Buchholz *et al.*, 2001; Johnstone *et al.*,
874 2005). This deserves more research, however, with more accurate measurement methods;
875 in the studies cited, residual variability was ~25% of REE, i.e., ~300-400 kcal/d (Wang *et al.*,
876 2011). Interestingly, women's AT is more metabolically active and ~10 fold more variable
877 than men's (Buchholz *et al.*, 2001). This is due in part to a 5-fold higher expression of UCP-1
878 in women's brown adipocytes (Nookaew *et al.*, 2013).
879
880 REE varies over the menstrual cycle, from a minimum in the early follicular phase to a
881 maximum ~50-100 kcal/d more in the luteal phase (Day *et al.*, 2005). Administration of a
882 GnRH antagonist during the mid-luteal phase reduced REE to the early-follicular level,
883 indicating a role of ovarian hormones (Day *et al.*, 2005). Progestins seem not to be involved
884 because high-progestin contraceptives have little effect on REE (Pelkman *et al.*, 2001).
885 Estrogens may be the cause because transdermal estrogen treatment increases REE in
886 premenopausal women in whom endogenous ovarian hormones are suppressed by GnRH
887 antagonism for either six days or five months (Day *et al.*, 2005; Melanson *et al.*, 2015; Van
888 Pelt *et al.*, 2015).
889
890 The effect of menopause on REE has not received much investigation. In one four-year
891 longitudinal study beginning with regularly cycling women at least 43 years of age, sleeping
892 REE decreased by 7.9% in the women who became postmenopausal during the study
893 compared with 5.3% in those who remained premenopausal, but the difference was not
894 statistically significant (Lovejoy *et al.*, 2008). In a two-week study of postmenopausal women,

estrogen treatment did not affect REE (Bessesen *et al.*, 2015). Three-month treatment with a selective estrogen-receptor agonist also failed to increase REE in ovariectomized old-world monkeys (Sullivan *et al.*, 2012). In contrast, estrogens clearly increase REE in laboratory rodents (Rogers *et al.*, 2009), and REE is decreased in *Esr1* knockout mice of both sexes, although not in *Esr2* knockouts (reviewed in (Mauvais-Jarvis, 2011; Van Pelt *et al.*, 2015)).

Dietary-induced thermogenesis (DIT)

Studies of reproductive hormonal effects on DIT are contradictory. DIT has been found to increase, decrease or not to change in the luteal phase of the menstrual cycle compared with the follicular phase (Li *et al.*, 1999; Melanson *et al.*, 1996; Piers *et al.*, 1995; Tai *et al.*, 1997). Estrogen treatment did not affect DIT in premenopausal women in whom endogenous ovarian hormones were suppressed by GnRH antagonism (Melanson *et al.*, 1996). We know of no studies of DIT across menopause.

Physical activity EE

Estrogens increase physical acivity in rats, mice and monkeys, but whether this is so in humans is unknown (Asarian and Geary, 2013). One study found that healthy-weight and overweight women walked ~1600 more steps/day (~100-200 kcal/d) during the early-follicular phase compared with the mid-luteal phase (Day *et al.*, 2005). It is interesting to note that physical-activity EE decreased during the luteal phase, whereas REE increased. Estrogen treatment did not affect physical-activity EE in premenopausal women in whom endogenous ovarian hormones were acutely suppressed by GnRH antagonists (Melanson *et al.*, 1996). Around the age of menopause, physical activity EE tends to decrease substantially, but similarly in women who become postmenopausal and those who do not (30 and 39%, respectively) (Lovejoy *et al.*, 2008). Even if menopause is not the cause, the magnitude of average decrease in physical-activity EE in aging women is clearly clinically relevant (Woolf *et al.*, 2008).

923 Surprisingly, most studies indicate that acute physical activity results in negative energy
924 balance, i.e., energy intake either does not change or is reduced following physical activity
925 EE (Blundell *et al.*, 2015; Deighton *et al.*, 2013; Howe *et al.*, 2014; King *et al.*, 2011). This
926 was recently confirmed in a study in which participants expended ~1.3 MET for two
927 consecutive days with no change in food intake (Douglas *et al.*, 2015). Why food deprivation
928 leads to compensatory eating in and acute physical activity does not is unknown (Blundell *et*
929 *al.*, 2010). Obviously, at some point regular moderate or high intensity physical activitiy EE
930 must lead to increase energy intake to avoid weight loss, but how this occurs is also
931 unknown (Stensel, 2010).
932
933 *Central mechanisms*
934 REE. Genetic and physiological studies in mice and rats indicate that estrogens acting via
935 *Esr1* in the ventromedial nucleus of the hypothalamus (VMN) increase EE by increasing
936 hypothalamic sympathetic outflow, resulting in increased brown-AT UCP-1 activity (Martínez
937 de Morentin *et al.*, 2014; Musatov *et al.*, 2007; Xu *et al.*, 2011). Because the animals were
938 maintained below thermoneutrality, however, it is difficult to distinguish REE from
939 thermoregulatory EE. Pronounced species differences also complicate EE research. For
940 example, glucocorticoids decrease brown-AT UCP-1 activity in mice, but stimulate it in
941 humans (Ramage *et al.*, 2016).
942
943 Physical activity. Female rats and mice are much more spontaneously active than their male
944 conspecifics. Estrogens appear to act in at least three brain areas to stimulate physical
945 activity in mice and rats. First, (Fahrbach *et al.*, 1985) found that estradiol injections into the
946 medial preoptic area increased physical activity in rats. Second, Musatov et al. (Musatov *et*
947 *al.*, 2007) found that knockdown of Esr1 in the VMH reduced physical activity in female rats.
948 Using complementary site-specific knockout and pharmacogenetic stimulation of Esr1,
949 Correa et al. (Correa *et al.*, 2015) demonstrated that VMH Esr1 neurons stimulate physical
950 activity in female, but not male, mice and are a distinct subpopulation not involved in

controlling eating, brown-AT activation or fertility, as indicated by the maturation of corpora lutea. Finally, using site-specific Esr1 knockout or knockdown, (Xu *et al*., 2015) found that Esr1 neurons in the medial nucleus of the amygdala also control physical activity, but do so similarly in male and female mice.

Physical activity-induced increases in EE affect activity of reward regions of the brain in humans. For example an escalating six month daily treadmill regimen reduced insula responses to highly valued food pictures (vs. non-food) in overweight and obese subjects in the fasted state, and this reduction in insula activation correlated with reduction in fat mass and body weight (Cornier *et al*., 2012; McFadden *et al*., 2013). Moreover, after acute sixty minute exercise, normal-weight subjects showed increased dorsolateral prefrontal activity and reduced insula, putamen, orbitofrontal, and hippocampal activity to pictures of high calorie food (vs. non-food) (Crabtree *et al*., 2014; Evero *et al*., 2012). These changes could explain the inhibitory effect of exercise on eating described above. In particular, exercise downregulates the food-related responses of cortical and subcortical reward regions and upregulates the responses of prefrontal control regions. However, how ovarian hormones influence the relation between exercise and central food processing remains largely unknown.

DISCUSSION

Obesity results from a tonically greater energy intake than EE. This simple truth belies the facts that the controls of eating and EE, the development of obesity, and the cardiometabolic consequences of the amount and distribution of AT are each multifactorial processes involving genetic, epigenetic, metabolic, endocrine, psychological, social and cultural factors, most of which are poorly understood. Because obesity remediation is a worldwide health challenge and because current strategies for weight reduction, other than bariatric surgery, have limited efficacy, there is an urgent need for research aimed at developing, first, further

preventive and therapeutic strategies to achieve and maintain healthy levels of adiposity, and second, to minimize cardiometabolic and other risks of increased adiposity. Physiological sex differences are important variables in these processes. This should be clear from the marked sex differerences in obesity prevalence, especially prevalence of severe obesity (BMI ≥ 35 kg/m^2).

We find that sex-specific physiological mechanisms, especially estrogen-mediated effects, play significant roles in the development of obesity in women as well as in its pathophysiological consequences. **Table 2** summarizes well established and probable female-specific obesity-related mechanisms, based on a wide variety of human and animal research. Estrogens act in the brain, in the AT and in other peripheral sites to affect (1) the proximal causes of obesity, i.e., relative increases in eating and decreases in EE, (2) the amount and regional distribution of AT, and (3) AT depot-specific pathophysiological changes that lead to morbidity. As a result, estrogens contribute both to male-female sex differences in obesity and obesity co-morbidities and to changes in obesity and obesity co-morbidities through women's lives **(Figure 5)**. Therefore, understanding the full impact of AT on women's health will require consideration of hormonal status on each of these processes. Currently astonishingly few data are available that address the normal physiology of these processes, much less the effects of surgical and hormonal treatments on female overweight and obesity or the pathophysiology of endocrine disorders with obesity as a frequent co-morbidity.

Many of the effects described in **Table 2** may appear to be small. For example, changes in food intake and EE through the menstrual cycle are on average only a few hundred kcal/d. It should be realized, however, that regular small changes in energy balance can lead to substantial differences in body weight and therefore be of considerable physiological relevance. The best available estimates indicate that an average increase of only 240 kcal/d in energy intake over EE is sufficient to produce the mean increase in average body weight

1007 that underlies the obesity epidemic in the USA (Hall *et al.*, 2011). Thus, the phenomena
1008 reviewed here are medically relevant and worthy of increased basic and clinical research.
1009
1010 It is also clear that obesity-related physiological characteristics vary widely across individual
1011 women. For example, as reviewed above, although most obese women display the female
1012 typical pattern of relatively more gluteofemoral AT than central AT, some women have male-
1013 typical, central AT distribution (Karpe and Pinnick, 2015). The effects of menstrual cycle on
1014 flavour preferences also display great inter-subject variability (Bartoshuk *et al.*, 1994; 2006).
1015 Such variability may arise for many reasons, ranging from psychological, social and cultural
1016 influences on one side to genetic and epigenetic effects on the other side (Shepard *et al.*,
1017 2009). Inter-subject variability together with the modest effect sizes mentioned above is a
1018 great challenge for research and an impediment to translation of research data into clinical
1019 practice. Research can meet this challenge in a variety of ways. Sample sizes should be
1020 based on power calculations taking effect size and variability into account. In addition,
1021 special care is required in sex research to consider subject characteristics, including age,
1022 race, ethanol use, stress levels or "allostatic load," psychological traits such as tendencies for
1023 emotional or binge eating, etc., that can alter the sex-specific influences on AT physiology,
1024 eating and EE. In such cases, appropriate statistical tools are helpful; for example, the
1025 multiple-regression analyses described above that parse the separate effects of aging and
1026 menopause on AT. Finally, researchers should avail themselves of the many methodological
1027 improvements that can increase the efficiency and meaning of pre-clinical and clinical sex-
1028 related research (Becker *et al.*, 2005; Greenspan *et al.*, 2007; Keitt *et al.*, 2003; McCarthy *et*
1029 *al.*, 2012; Rubinow and Schmidt, 2002).
1030
1031 The homogeneity of study groups with respect to reproductive physiology status itself is
1032 another important issue that often is overlooked, in part because findings in one domain fail
1033 to reach researchers in other domains. This is one of many reasons that inter-disciplinary
1034 investigator groups should be facilitated. Thus, post-menopausal study participants should

be characterized, menstrual cycles should be evaluated more accurately in both obese and non-obese women, and effects of the type and duration of HT, including the interval between menopause and beginning HT, should be assessed. In women with surgical menopause, the indication for ovariectomy and whether hysterectomy was also done should be considered. In addition, as it is likely that indications for gynaecological surgery differ in obese and non-obese women, due, for example to the higher prevalence of endometrial cancer and disturbed bleeding patterns in obese women (Crujeiras and Casanueva, 2015; Madsen *et al.*, 2013), associations between surgical menopause and adiposity and AT distribution need to be explored. A related issue is that reproductive physiology, in particular estrogens, also may influence experimental outcomes via "off-target" physiological functions. For example, pharmacological data in women may be influenced by differences in the bioactivity of many drugs due to sex differences in cytochrome p450 enzyme activity, effects of estrogens on hepatic drug metabolism, and effects of estrogens on plasma levels of sex-hormone binding globulin and other globulins (Soldin and Mattison, 2009; Spoletini *et al.*, 2012).

We acknowledge weaknesses of the review. We focused on the classical AT depots, although excess adiposity is also associated with increased hepatic, intramuscular and cardiovascular fat, which are independently associated with cardiometabolic risk and appear to be affected by hormonal status in women (Khoudary *et al.*, 2015; Marino and Jornayvaz, 2015; Oosthuyse and Bosch, 2012). We focused mainly on preclinical whole-body mechanistic studies, at the expense of detailed reviews of cell- and tissue-level studies, genome-wide gene association studies, and epidemiological studies, despite the many plausible mechanistic hypotheses that these suggest. We did not consider pregnancy, although postpartum weight gain is an important obesity risk (Gore *et al.*, 2003). We did not consider tissue-specific synthesis of estrogens in the brain or AT or production of neurally active estrogen metabolites or other neurosteroids (Azcoitia *et al.*, 2011; Do Rego *et al.*, 2012; Porcu *et al.*, 2016).

In conclusion, current human and animal research supports significant roles of ovarian hormones, especially estrogens, in the regulation of female AT. These involve influences on eating, EE, AT amount, regional AT distribution and the physiological function of adipocytes in the various AT depots. In the coming years, improvements in research design and analyses and the development of additional powerful methodologies should lead to important progress across the range of diverse influences of female physiology on adiposity. Continued animal research should better characterize, for example, the site and nature of estrogen receptors in the brain that affect eating and EE. Animal research should also lead the way to identifying the downstream molecular mechanisms responding to the activation of estrogen response elements in the DNA, which contribute the hormone's effects on gluteofemoral AT and on most, if not all, of its neural effects. A pressing issue in this connection is the better understanding of the interaction of estrogenic and genetic controls leading to the protective cardiometabolic effects of gluteofemoral AT. Similarly, improvements in the design of fMRI studies should help specify the neural information-processing mechanisms underlying sex-related hedonic and cognitive controls of eating. Progress in these and other research directions described here should lead to better understanding of female obesity, including clinically challenging syndromes such as PCOS and, ultimately, to better strategies to maintain and improve women's health in the face of the obesity epidemic.

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References

Abdulnour J, Doucet E, Brochu M, Lavoie J-M, Strychar I, Rabasa-Lhoret R, Prud'homme D. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. *Menopause* 2012;**19**:760–767.

Aguiar AL, Couto-Silva AC, Vicente EJ, Freitas IC, Cruz T, Adan L. Weight evolution in girls treated for idiopathic central precocious puberty with GnRH analogues. *J Pediatr Endocrinol Metab* 2006;**19**:1327–1334.

Almey A, Milner TA, Brake WG. Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. *Horm Behav* 2015;**74**:125–138.

Alonso-Alonso MM, Ziemke FF, Magkos FF, Barrios FAF, Brinkoetter MM, Boyd II, Rifkin-Graboi AA, Yannakoulia MM, Rojas RR, Pascual-Leone AA, *et al.* Brain responses to food images during the early and late follicular phase of the menstrual cycle in healthy young women: relation to fasting and feeding. *Am J Clin Nutr* 2011;**94**:377–384.

Arem H, Keadle SK, Matthews CE. Invited commentary: meta-physical activity and the search for the truth. *Am J Epidemiol* 2015;**181**:656–658.

Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, *et al.* Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015;**175**:959–967.

Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, Buchholz BA, Eriksson M, Arner E, Hauner H, *et al.* Dynamics of human adipose lipid turnover in health and metabolic disease. *Nature* 2011;**478**:110–113.

Asarian L, Geary N. Sex differences in the physiology of eating. *Am J Physiol Regul Integr Comp Physiol* 2013;**305**:R1215–67.

ASHRAE: American Society of Heating, Refrigerating and Air-Conditioning Engineers, https://www.ashrae.org/resources--publications/bookstore/standard-55, downloaded March 2016.

Azcoitia I, Yague JG, Garcia-Segura LM. Estradiol synthesis within the human brain. *Neuroscience* 2011;**191**:139–147.

1132 Barber TM, Golding SJ, Alvey C, Wass JAH, Karpe F, Franks S, McCarthy MI. Global
1133 adiposity rather than abnormal regional fat distribution characterizes women with
1134 polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;**93**:999–1004.

1135 Barr SI, Janelle KC, Prior JC. Energy intakes are higher during the luteal phase of ovulatory
1136 menstrual cycles. *Am J Clin Nutr* 1995;**61**:39–43.

1137 Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause
1138 mortality: a meta-analysis. *Prog Cardiovasc Dis* 2014;**56**:382–390.

1139 Bartoshuk LM, Duffy VB, Hayes JE, Moskowitz HR, Snyder DJ. Psychophysics of sweet and
1140 fat perception in obesity: problems, solutions and new perspectives. *Philos Trans R Soc*
1141 *Lond, B, Biol Sci* 2006;**361**:1137–1148.

1142 Bartoshuk LM, Duffy VB, Miller IJ. PTC/PROP tasting: anatomy, psychophysics, and sex
1143 effects. *Physiol Behav* 1994;**56**:1165–1171.

1144 Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in
1145 response to food among adolescent girls: an fMRI study. *Neuroimage* 2010;**52**:1696–
1146 1703.

1147 Becker JB, Arnold AP, Berkley KJ, Blaustein JD, Eckel LA, Hampson E, Herman JP, Marts
1148 S, Sadee W, Steiner M, *et al.* Strategies and methods for research on sex differences in
1149 brain and behavior. *Endocrinology* 2005;**146**:1650–1673.

1150 Bellino FL, Wise PM. Nonhuman primate models of menopause workshop. In: Vol 68. 2003,
1151 10–18.

1152 Belzer LM, Smulian JC, Lu S-E, Tepper BJ. Food cravings and intake of sweet foods in
1153 healthy pregnancy and mild gestational diabetes mellitus. A prospective study. *Appetite*
1154 2010;**55**:609–615.

1155 Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and
1156 women to anorexigenic and memory-improving effects of intranasal insulin. *J Clin*
1157 *Endocrinol Metab* 2008;**93**:1339–1344.

1158 Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, Hucking K, Ader M. Why
1159 visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity (Silver Spring)*
1160 2006;**14 Suppl 1**:16S–19S.

1161 Berthoud H-R. Multiple neural systems controlling food intake and body weight. *Neurosci*
1162 *Biobehav Rev* 2002;**26**:393–428.

1163 Bessesen DH, Cox-York KA, Hernandez TL, Erickson CB, Wang H, Jackman MR, Van Pelt
1164 RE. Postprandial triglycerides and adipose tissue storage of dietary fatty acids: impact of
1165 menopause and estradiol. *Obesity (Silver Spring)* 2015;**23**:145–153.

1166 Betley JN, Xu S, Cao ZFH, Gong R, Magnus CJ, Yu Y, Sternson SM. Neurons for hunger
1167 and thirst transmit a negative-valence teaching signal. *Nature* 2015;**521**:180–185.

1168 Biebermann H, Kühnen P, Kleinau G, Krude H. The neuroendocrine circuitry controlled by
1169 POMC, MSH, and AGRP. *Handb Exp Pharmacol* 2012;**209**:47–75.

1170 Blenck CL, Harvey PA, Reckelhoff JF, Leinwand LA. The Importance of Biological Sex and
1171 Estrogen in Rodent Models of Cardiovascular Health and Disease. *Circ Res*
1172 2016;**118**:1294–1312.

1173 Blouin K, Nadeau M, Perreault M, Veilleux A, Drolet R, Marceau P, Mailloux J, Luu-The V,
1174 Tchernof A. Effects of androgens on adipocyte differentiation and adipose tissue explant
1175 metabolism in men and women. *Clinical Endocrinology* 2010;**72**:176–188.

1176 Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, Mela D, Salah S, Schuring
1177 E, van der Knaap H, *et al.* Appetite control: methodological aspects of the evaluation of
1178 foods. *Obes Rev* 2010;**11**:251–270.

1179 Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M. Appetite control and energy
1180 balance: impact of exercise. *Obes Rev* 2015;**16 Suppl 1**:67–76.

1181 Boucher JG, Husain M, Rowan-Carroll A, Williams A, Yauk CL, Atlas E. Identification of
1182 mechanisms of action of bisphenol a-induced human preadipocyte differentiation by
1183 transcriptional profiling. *Obesity (Silver Spring)* 2014;**22**:2333–2343.

1184 Bowen DJ, Grunberg NE. Variations in food preference and consumption across the
1185 menstrual cycle. *Physiol Behav* 1990;**47**:287–291.

1186 Brennan IM, Feltrin KL, Nair NS, Hausken T, Little TJ, Gentilcore D, Wishart JM, Jones KL,
1187 Horowitz M, Feinle-Bisset C. Effects of the phases of the menstrual cycle on gastric
1188 emptying, glycemia, plasma GLP-1 and insulin, and energy intake in healthy lean
1189 women. *Am J Physiol Gastrointest Liver Physiol* 2009;**297**:G602–10.

1190 Brinton RD, Thompson RF, Foy MR, Baudry M, Wang J, Finch CE, Morgan TE, Pike CJ,
1191 Mack WJ, Stanczyk FZ, *et al.* Progesterone receptors: form and function in brain. *Front*
1192 *Neuroendocrinol* 2008;**29**:313–339.

1193 Brüning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W,
1194 Müller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and
1195 reproduction. *Science* 2000;**289**:2122–2125.

1196 Buchholz AC, Rafii M, Pencharz PB. Is resting metabolic rate different between men and
1197 women? *Br J Nutr* 2001;**86**:641–646.

1198 Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, Ravussin E,
1199 Ryan DH, Smith SR, Katzmarzyk PT. The relationship of waist circumference and BMI to
1200 visceral, subcutaneous, and total body fat: sex and race differences. *Obesity (Silver*
1201 *Spring)* 2011;**19**:402–408.

1202 Camilleri M. Peripheral mechanisms in appetite regulation. *Gastroenterology*
1203 2015;**148**:1219–1233.

1204 Cao L, Choi EY, Liu X, Martin A, Wang C, Xu X, During MJ. White to brown fat phenotypic
1205 switch induced by genetic and environmental activation of a hypothalamic-adipocyte
1206 axis. *Cell Metab* 2011;**14**:324–338.

1207 Cao X, Xu P, Oyola MG, Xia Y, Yan X, Saito K, Zou F, Wang C, Yang Y, Hinton A, *et al.*
1208 Estrogens stimulate serotonin neurons to inhibit binge-like eating in mice. *J Clin Invest*
1209 2014;**124**:4351–4362.

1210 Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, Di Fede G, Rini G.
1211 Abdominal fat quantity and distribution in women with polycystic ovary syndrome and
1212 extent of its relation to insulin resistance. *J Clin Endocrinol Metab* 2007;**92**:2500–2505.

1213 Carmina E, Bucchieri S, Mansueto P, Rini G, Ferin M, Lobo RA. Circulating levels of adipose
1214 products and differences in fat distribution in the ovulatory and anovulatory phenotypes
1215 of polycystic ovary syndrome. *Fertil Steril* 2009;**91**:1332–1335.

1216 Carmina E, Chu MC, Moran C, Tortoriello D, Vardhana P, Tena G, Preciado R, Lobo R.
1217 Subcutaneous and omental fat expression of adiponectin and leptin in women with
1218 polycystic ovary syndrome. *Fertil Steril* 2008;**89**:642–648.

1219 Castro DC, Berridge KC. Advances in the neurobiological bases for food 'liking' versus
1220 'wanting'. *Physiol Behav* 2014;**136**:22–30.

1221 Chazenbalk G, Trivax BS, Yildiz BO, Bertolotto C, Mathur R, Heneidi S, Azziz R. Regulation
1222 of adiponectin secretion by adipocytes in the polycystic ovary syndrome: role of tumor
1223 necrosis factor-{alpha}. *J Clin Endocrinol Metab* 2010;**95**:935–942.

1224 Chen X, McClusky R, Chen J, Beaven SW, Tontonoz P, Arnold AP, Reue K. The number of
1225 x chromosomes causes sex differences in adiposity in mice. Attie A (ed). *PLoS Genet*
1226 2012;**8**:e1002709.

1227 Chen Y, Heiman ML. Increased weight gain after ovariectomy is not a consequence of leptin
1228 resistance. *Am J Physiol Endocrinol Metab* 2001;**280**:E315–22.

1229 Clark MK, Dillon JS, Sowers M, Nichols S. Weight, fat mass, and central distribution of fat
1230 increase when women use depot-medroxyprogesterone acetate for contraception. *Int J*
1231 *Obes (Lond)* 2005;**29**:1252–1258.

1232 Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to
1233 central leptin and insulin. *Diabetes* 2006;**55**:978–987.

1234 Clegg DJ, Brown LM, Zigman JM, Kemp CJ, Strader AD, Benoit SC, Woods SC,
1235 Mangiaracina M, Geary N. Estradiol-dependent decrease in the orexigenic potency of
1236 ghrelin in female rats. *Diabetes* 2007;**56**:1051–1058.

1237 Clegg DJ, Riedy CA, Smith KAB, Benoit SC, Woods SC. Differential sensitivity to central
1238 leptin and insulin in male and female rats. *Diabetes* 2003;**52**:682–687.

1239 Collins S. A heart-adipose tissue connection in the regulation of energy metabolism. *Nat Rev*
1240 *Endocrinol* 2014;**10**:157–163.

1241 Cornier M-A, Melanson EL, Salzberg AK, Bechtell JL, Tregellas JR. The effects of exercise
1242 on the neuronal response to food cues. *Physiol Behav* 2012;**105**:1028–1034.

1243 Cornier M-A, Salzberg AK, Endly DC, Bessesen DH, Tregellas JR. Sex-based differences in
1244 the behavioral and neuronal responses to food. *Physiol Behav* 2010;**99**:538–543.

1245 Correa SM, Newstrom DW, Warne JP, Flandin P, Cheung CC, Lin-Moore AT, Pierce AA, Xu
1246 AW, Rubenstein JL, Ingraham HA. An estrogen-responsive module in the ventromedial
1247 hypothalamus selectively drives sex-specific activity in females. *Cell Rep* 2015;**10**:62–74.

1248 Crabtree DR, Chambers ES, Hardwick RM, Blannin AK. The effects of high-intensity exercise
1249 on neural responses to images of food. *Am J Clin Nutr* 2014;**99**:258–267.

1250 Cristancho AG, Lazar MA. Forming functional fat: a growing understanding of adipocyte
1251 differentiation. *Nat Rev Mol Cell Biol* 2011;**12**:722–734.

1252 Crujeiras AB, Casanueva FF. Obesity and the reproductive system disorders: epigenetics as
1253 a potential bridge. *Hum Reprod Update* 2015;**21**:249–261.

1254 Culbert KM, Racine SE, Klump KL. Hormonal Factors and Disturbances in Eating Disorders.
1255 *Curr Psychiatry Rep* 2016;**18**:65–16.

1256 Czaja JA. Ovarian influences on primate food intake: assessment of progesterone actions.
1257 *Physiol Behav* 1978;**21**:923–928.

1258 D'Alessio DA, Kavle EC, Mozzoli MA, Smalley KJ, Polansky M, Kendrick ZV, Owen LR,
1259 Bushman MC, Boden G, Owen OE. Thermic effect of food in lean and obese men. *J Clin*
1260 *Invest* 1988;**81**:1781–1789.

1261 Dal'Ava N, Bahamondes L, Bahamondes MV, Bottura BF, Monteiro I. Body weight and body
1262 composition of depot medroxyprogesterone acetate users. *Contraception* 2014;**90**:182–
1263 187.

1264 Dalgaard K, Landgraf K, Heyne S, Lempradl A, Longinotto J, Gossens K, Ruf M, Orthofer M,
1265 Strogantsev R, Selvaraj M, *et al.* Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic
1266 Obesity. *Cell* 2016;**164**:353–364.

1267 Davis C. The epidemiology and genetics of binge eating disorder (BED). *CNS Spectr*
1268 2015;**20**:522–529.

1269 Davis KE, D Neinast M, Sun K, M Skiles W, D Bills J, A Zehr J, Zeve D, D Hahner L, W Cox
1270 D, M Gent L, *et al.* The sexually dimorphic role of adipose and adipocyte estrogen
1271 receptors in modulating adipose tissue expansion, inflammation, and fibrosis. *Mol Metab*
1272 2013;**2**:227–242.

1273 Day DS, Gozansky WS, Van Pelt RE, Schwartz RS, Kohrt WM. Sex hormone suppression
1274 reduces resting energy expenditure and {beta}-adrenergic support of resting energy
1275 expenditure. *J Clin Endocrinol Metab* 2005;**90**:3312–3317.

1276 DeClercq V, Taylor C, Zahradka P. Adipose tissue: the link between obesity and
1277 cardiovascular disease. *Cardiovasc Hematol Disord Drug Targets* 2008;**8**:228–237.

1278 Deighton K, Barry R, Connon CE, Stensel DJ. Appetite, gut hormone and energy intake
1279 responses to low volume sprint interval and traditional endurance exercise. *Eur J Appl*
1280 *Physiol* 2013;**113**:1147–1156.

1281 Dempfle A, Hinney A, Heinzel-Gutenbrunner M, Raab M, Geller F, Gudermann T, Schäfer H,
1282 Hebebrand J. Large quantitative effect of melanocortin-4 receptor gene mutations on
1283 body mass index. *J Med Genet* 2004;**41**:795–800.

1284 Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;**444**:881–
1285 887.

1286 Dhurandhar EJ, Kaiser KA, Dawson JA, Alcorn AS, Keating KD, Allison DB. Predicting adult
1287 weight change in the real world: a systematic review and meta-analysis accounting for
1288 compensatory changes in energy intake or expenditure. *Int J Obes (Lond)*
1289 2015;**39**:1181–1187.

1290 Diamanti-Kandarakis E. Role of obesity and adiposity in polycystic ovary syndrome. *Int J*
1291 *Obes (Lond)* 2007;**31 Suppl 2**:S8–13– discussion S31–2.

1292 Dillard TH, Purnell JQ, Smith MD, Raum W, Hong D, Laut J, Patterson EJ. Omentectomy
1293 added to Roux-en-Y gastric bypass surgery: a randomized, controlled trial. *Surg Obes*
1294 *Relat Dis* 2013;**9**:269–275.

1295 Do Rego JL, Seong JY, Burel D, Leprince J, Vaudry D, Luu-The V, Tonon M-C, Tsutsui K,
1296 Pelletier G, Vaudry H. Regulation of neurosteroid biosynthesis by neurotransmitters and
1297 neuropeptides. *Front Endocrinol (Lausanne)* 2012;**3**:4.

1298 Douglas JA, King JA, McFarlane E, Baker L, Bradley C, Crouch N, Hill D, Stensel DJ.
1299 Appetite, appetite hormone and energy intake responses to two consecutive days of
1300 aerobic exercise in healthy young men. *Appetite* 2015;**92**:57–65.

1301 Dreher J-C, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase
1302 modulates reward-related neural function in women. *Proc Natl Acad Sci USA*
1303 2007;**104**:2465–2470.

1304 Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific
1305 Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular
1306 Genetics of Polycystic Ovary Syndrome. *Endocrine Reviews* 2015;**36**:487–525.

1307 Eck LH, Bennett AG, Egan BM, Ray JW, Mitchell CO, Smith MA, Klesges RC. Differences in
1308 macronutrient selections in users and nonusers of an oral contraceptive. *Am J Clin Nutr*
1309 1997;**65**:419–424.

1310 Escobar-Morreale HF, San Millán JL. Abdominal adiposity and the polycystic ovary
1311 syndrome. *Trends Endocrinol Metab* 2007;**18**:266–272.

1312 Evero N, Hackett LC, Clark RD, Phelan S, Hagobian TA. Aerobic exercise reduces neuronal
1313 responses in food reward brain regions. *J Appl Physiol* 2012;**112**:1612–1619.

1314 Fahrbach SE, Meisel RL, Pfaff DW. Preoptic implants of estradiol increase wheel running but
1315 not the open field activity of female rats. *Physiol Behav* 1985;**35**:985–992.

1316 Farr OM, Li C-SR, Mantzoros CS. Central nervous system regulation of eating: Insights from
1317 human brain imaging. *Metab Clin Exp* 2016;**65**:699–713.

1318 Fields DA, Gunatilake R, Kalaitzoglou E. Air displacement plethysmography: cradle to grave.
1319 *Nutr Clin Pract* 2015;**30**:219–226.

1320 Fong AK, Kretsch MJ. Changes in dietary intake, urinary nitrogen, and urinary volume across
1321 the menstrual cycle. *Am J Clin Nutr* 1993;**57**:43–46.

1322 Ford ES, Merritt RK, Heath GW, Powell KE, Washburn RA, Kriska A, Haile G. Physical
1323 activity behaviors in lower and higher socioeconomic status populations. *Am J Epidemiol*
1324 1991;**133**:1246–1256.

1325 Frank TC, Kim GL, Krzemien A, Van Vugt DA. Effect of menstrual cycle phase on
1326 corticolimbic brain activation by visual food cues. *Brain Res* 2010;**1363**:81–92.

1327 Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution
1328 with menopause. *Metab Clin Exp* 2009;**58**:311–315.

1329 Freeman EW, Sammel MD, Lin H, Gracia CR. Obesity and reproductive hormone levels in
1330 the transition to menopause. *Menopause* 2010;**17**:718–726.

1331 French SA, Epstein LH, Jeffery RW, Blundell JE, Wardle J. Eating behavior dimensions.
1332 Associations with energy intake and body weight. A review. *Appetite* 2012;**59**:541–549.

1333 Fried SK, Lee M-J, Karastergiou K. Shaping fat distribution: New insights into the molecular
1334 determinants of depot- and sex-dependent adipose biology. *Obesity (Silver Spring)*
1335 2015;**23**:1345–1352.

1336 Friedl F, Riedl D, Fessler S, Wildt L, Walter M, Richter R, Schüßler G, Böttcher B. Impact of
1337 endometriosis on quality of life, anxiety, and depression: an Austrian perspective. *Arch*
1338 *Gynecol Obstet* 2015.

1339 Fromme T, Klingenspor M. Uncoupling protein 1 expression and high-fat diets. *Am J Physiol*
1340 *Regul Integr Comp Physiol* 2011;**300**:R1–8.

1341 Fu J, Hofker M, Wijmenga C. Apple or pear: size and shape matter. *Cell Metab*
1342 2015;**21**:507–508.

1343 Furlong TM, Jayaweera HK, Balleine BW, Corbit LH. Binge-like consumption of a palatable
1344 food accelerates habitual control of behavior and is dependent on activation of the
1345 dorsolateral striatum. *J Neurosci* 2014;**34**:5012–5022.

1346 Gabrielsson BG, Johansson JM, Lönn M, Jernås M, Olbers T, Peltonen M, Larsson I, Lönn L,
1347 Sjöström L, Carlsson B, *et al.* High expression of complement components in omental
1348 adipose tissue in obese men. *Obes Res* 2003;**11**:699–708.

1349 Gallagher D, Kuznia P, Heshka S, Albu J, Heymsfield SB, Goodpaster B, Visser M, Harris
1350 TB. Adipose tissue in muscle: a novel depot similar in size to visceral adipose tissue. *Am*
1351 *J Clin Nutr* 2005;**81**:903–910.

1352 Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is
1353 body mass index for comparison of body fatness across age, sex, and ethnic groups?
1354 *Am J Epidemiol* 1996;**143**:228–239.

1355 Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination
1356 contraceptives: effects on weight. Lopez LM (ed). *Cochrane Database Syst Rev*
1357 2014:CD003987.

1358 Gambacciani M, Ciaponi M, Cappagli B, Benussi C, De Simone L, Genazzani AR.
1359 Climacteric modifications in body weight and fat tissue distribution. *Climacteric*
1360 1999;**2**:37–44.

1361 Geary N, Moran TH. Appetite. In: *Comprehensive Textbook of Psychiatry*, 10th Edition,
1362 Benjamin J. Sadock, Virginia A. Sadock, and Pedro Ruiz, editors. Philadelphia PA USA:
1363 Lippincott Williams & Wilkens, 2016 (in press).

1364 Geliebter A, Pantazatos SP, McOuatt H, Puma L, Gibson CD, Atalayer D. Sex-based fMRI
1365 differences in obese humans in response to high vs. low energy food cues. *Behav Brain*
1366 *Res* 2013;**243**:91–96.

1367 Gesta S, Blüher M, Yamamoto Y, Norris AW, Berndt J, Kralisch S, Boucher J, Lewis C, Kahn
1368 CR. Evidence for a role of developmental genes in the origin of obesity and body fat
1369 distribution. *Proc Natl Acad Sci USA* 2006;**103**:6676–6681.

1370 Gilliat-Wimberly M, Manore MM, Woolf K, Swan PD, Carroll SS. Effects of habitual physical
1371 activity on the resting metabolic rates and body compositions of women aged 35 to 50
1372 years. *J Am Diet Assoc* 2001;**101**:1181–1188.

1373 Goh LGH, Dhaliwal SS, Welborn TA, Lee AH, Della PR. Anthropometric measurements of
1374 general and central obesity and the prediction of cardiovascular disease risk in women: a
1375 cross-sectional study. *BMJ Open* 2014;**4**:e004138–e004138.

1376 Gong EJ, Garrel D, Calloway DH. Menstrual cycle and voluntary food intake. *Am J Clin Nutr*
1377 1989;**49**:252–258.

1378 Gore SA, Brown DM, West DS. The role of postpartum weight retention in obesity among
1379 women: a review of the evidence. *Ann Behav Med* 2003;**26**:149–159.

1380 Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS,
1381 Holdcroft A, Lautenbacher S, Mayer EA, *et al.* Studying sex and gender differences in
1382 pain and analgesia: a consensus report. In: Vol 132 Suppl 1. 2007, S26–45.

1383 Grill HJ, Hayes MR. Hindbrain neurons as an essential hub in the neuroanatomically
1384 distributed control of energy balance. *Cell Metab* 2012;**16**:296–309.

1385 Głab E, Barg E, Wikiera B, Grabowski M, Noczyńska A. Influence of GnRH analog therapy
1386 on body mass in central precocious puberty. *Pediatr Endocrinol Diabetes Metab*
1387 2009;**15**:7–11.

1388 Haines DE. Fundamental Neuroscience for Basic and Clinical Applications. 3rd ed. 2012.
1389 Philadelphia: Churchill Livingstone/Elsevier.
1390
1391 Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, Swinburn BA.
1392 Quantification of the effect of energy imbalance on bodyweight. *Lancet* 2011;**378**:826–
1393 837.

1394 Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H. Postprandial administration of intranasal
1395 insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes*
1396 2012;**61**:782–789.

1397 Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen Effects on Cognitive and Synaptic
1398 Health Over the Lifecourse. *Physiological Reviews* 2015;**95**:785–807.

1399 Hayes JE, Duffy VB. Oral sensory phenotype identifies level of sugar and fat required for
1400 maximal liking. *Physiol Behav* 2008;**95**:77–87.

1401 Herbison A. Physiology of the Gonadotropin-Releasing Hormone Neuronal Network. In:
1402 *Knobil and Neill's Physiology of Reproduction*.Vol 1. Elsevier, 2006, 1415–1482.

1403 Higgs S, Robinson E, Lee M. Learning and Memory Processes and Their Role in Eating:
1404 Implications for Limiting Food Intake in Overeaters. *Curr Obes Rep* 2012;**1**:91–98.

1405 Hilbert A, de Zwaan M, Braehler E. How frequent are eating disturbances in the population?
1406 Norms of the eating disorder examination-questionnaire. Tomé D (ed). *PLoS ONE*
1407 2012;**7**:e29125.

1408 Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition:
1409 a prospective study in Chinese perimenopausal women. *Int J Obes (Lond)*
1410 2010;**34**:1265–1274.

1411 Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M,
1412 Dustin L, Kono N, *et al.* Vascular Effects of Early versus Late Postmenopausal
1413 Treatment with Estradiol. *N Engl J Med* 2016;**374**:1221–1231.

1414 Horstmann A, Kovacs P, Kabisch S, Boettcher Y, Schloegl H, Tönjes A, Stumvoll M, Pleger
1415 B, Villringer A. Common genetic variation near MC4R has a sex-specific impact on
1416 human brain structure and eating behavior. Esteban FJ (ed). *PLoS ONE* 2013;**8**:e74362.

1417 Howe SM, Hand TM, Manore MM. Exercise-trained men and women: role of exercise and
1418 diet on appetite and energy intake. *Nutrients* 2014;**6**:4935–4960.

1419 Hulbert AJ, Else PL. Membranes and the setting of energy demand. *J Exp Biol*
1420 2005;**208**:1593–1599.

1421 Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W,
1422 Kesterson RA, Boston BA, Cone RD, *et al.* Targeted disruption of the melanocortin-4
1423 receptor results in obesity in mice. *Cell* 1997;**88**:131–141.

1424 Item F, Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. *Obes*
1425 *Rev* 2012;**13 Suppl 2**:30–39.

1426 Jankowski M, Rachelska G, Donghao W, McCann SM, Gutkowska J. Estrogen receptors
1427 activate atrial natriuretic peptide in the rat heart. *Proc Natl Acad Sci USA*
1428 2001;**98**:11765–11770.

1429 Joffe H, Petrillo LF, Koukopoulos A, Viguera AC, Hirschberg A, Nonacs R, Somley B,
1430 Pasciullo E, White DP, Hall JE, *et al.* Increased estradiol and improved sleep, but not hot
1431 flashes, predict enhanced mood during the menopausal transition. *J Clin Endocrinol*
1432 *Metab* 2011;**96**:E1044–54.

1433 Johnstone AM, Murison SD, Duncan JS, Rance KA, Speakman JR. Factors influencing
1434 variation in basal metabolic rate include fat-free mass, fat mass, age, and circulating
1435 thyroxine but not sex, circulating leptin, or triiodothyronine. *Am J Clin Nutr* 2005;**82**:941–
1436 948.

1437 Justice AJ, de Wit H. Acute effects of d-amphetamine during the follicular and luteal phases
1438 of the menstrual cycle in women. *Psychopharmacology (Berl)* 1999;**145**:67–75.

1439 Kamel EG, McNeill G, Van Wijk MC. Usefulness of anthropometry and DXA in predicting
1440 intra-abdominal fat in obese men and women. *Obes Res* 2000;**8**:36–42.

1441 Kanaley JA, Sames C, Swisher L, Swick AG, Ploutz-Snyder LL, Steppan CM, Sagendorf KS,
1442 Feiglin D, Jaynes EB, Meyer RA, *et al.* Abdominal fat distribution in pre- and
1443 postmenopausal women: The impact of physical activity, age, and menopausal status.
1444 *Metab Clin Exp* 2001;**50**:976–982.

1445 Karastergiou K, Fried SK, Xie H, Lee M-J, Divoux A, Rosencrantz MA, Chang RJ, Smith SR.
1446 Distinct developmental signatures of human abdominal and gluteal subcutaneous
1447 adipose tissue depots. *J Clin Endocrinol Metab* 2013;**98**:362–371.

1448 Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue--link to whole-
1449 body phenotypes. *Nat Rev Endocrinol* 2015;**11**:90–100.

1450 Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, Ergun DL. Dual-
1451 energy X-ray absorptiometry for quantification of visceral fat. *Obesity (Silver Spring)*
1452 2012;**20**:1313–1318.

1453 Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk,
1454 Pathophysiology and Complications of Type 2 Diabetes Mellitus. *Endocrine Reviews*
1455 2016;**37**:278–316.

1456 Keen-Rhinehart E, Desai M, Ross MG. Central insulin sensitivity in male and female juvenile
1457 rats. *Horm Behav* 2009;**56**:275–280.

1458 Keitt SK, Wagner CR, Tong C, Marts SA. Understanding the biology of sex and gender
1459 differences: using subgroup analysis and statistical design to detect sex differences in
1460 clinical trials. *MedGenMed* 2003;**5**:39.

1461 Khoudary El SR, Shields KJ, Janssen I, Hanley C, Budoff MJ, Barinas-Mitchell E, Everson-
1462 Rose SA, Powell LH, Matthews KA. Cardiovascular Fat, Menopause, and Sex Hormones
1463 in Women: The SWAN Cardiovascular Fat Ancillary Study. *J Clin Endocrinol Metab*
1464 2015;**100**:3304–3312.

1465 Kiernan M, Winkleby MA. Identifying patients for weight-loss treatment: an empirical
1466 evaluation of the NHLBI obesity education initiative expert panel treatment
1467 recommendations. *Arch Intern Med* 2000;**160**:2169–2176.

1468 Kim JS, Rizwan MZ, Clegg DJ, Anderson GM. Leptin Signaling Is Not Required for
1469 Anorexigenic Estradiol Effects in Female Mice. *Endocrinology* 2016;**157**:1991–2001.

1470 King JA, Wasse LK, Ewens J, Crystallis K, Emmanuel J, Batterham RL, Stensel DJ.
1471 Differential acylated ghrelin, peptide YY3-36, appetite, and food intake responses to
1472 equivalent energy deficits created by exercise and food restriction. *J Clin Endocrinol*
1473 *Metab* 2011;**96**:1114–1121.

1474 Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R, Association for
1475 Weight Management and Obesity Prevention, NAASO, The Obesity Society, American
1476 Society for Nutrition, *et al.* Waist circumference and cardiometabolic risk: a consensus
1477 statement from Shaping America's Health: Association for Weight Management and
1478 Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition;
1479 and the American Diabetes Association. In: Vol 85. 2007, 1197–1202.

1480 Klump KL, Keel PK, Sisk C, Burt SA. Preliminary evidence that estradiol moderates genetic
1481 influences on disordered eating attitudes and behaviors during puberty. *Psychol Med*
1482 2010;**40**:1745–1753.

1483 Klump KL, Racine S, Hildebrandt B, Sisk CL. Sex differences in binge eating patterns in male
1484 and female adult rats. *Int J Eat Disord* 2013;**46**:729–736.

1485 Klump KL, Racine SE, Hildebrandt B, Burt SA, Neale M, Sisk CL, Boker S, Keel PK. Ovarian
1486 Hormone Influences on Dysregulated Eating: A Comparison of Associations in Women
1487 with versus without Binge Episodes. *Clin Psychol Sci* 2014;**2**:545–559.

1488 Ko JH, Lee HS, Lim JS, Kim SM, Hwang JS. Changes in bone mineral density and body
1489 composition in children with central precocious puberty and early puberty before and
1490 after one year of treatment with GnRH agonist. *Hormone Research in Paediatrics*
1491 2011;**75**:174–179.

1492 Konarzewski M, Książek A. Determinants of intra-specific variation in basal metabolic rate. *J*
1493 *Comp Physiol B, Biochem Syst Environ Physiol* 2013;**183**:27–41.

1494 Koren D, Marcus CL, Kim C, Gallagher PR, Schwab R, Bradford RM, Zemel BS.
1495 Anthropometric predictors of visceral adiposity in normal-weight and obese adolescents.
1496 *Pediatr Diabetes* 2013;**14**:575–584.

1497 Koster A, Stenholm S, Alley DE, Kim LJ, Simonsick EM, Kanaya AM, Visser M, Houston DK,
1498 Nicklas BJ, Tylavsky FA, *et al.* Body fat distribution and inflammation among obese older
1499 adults with and without metabolic syndrome. *Obesity (Silver Spring)* 2010;**18**:2354–2361.

1500 Koutsari C, Ali AH, Mundi MS, Jensen MD. Storage of circulating free fatty acid in adipose
1501 tissue of postabsorptive humans: quantitative measures and implications for body fat
1502 distribution. *Diabetes* 2011;**60**:2032–2040.

1503 Krashes MJ, Shah BP, Koda S, Lowell BB. Rapid versus delayed stimulation of feeding by
1504 the endogenously released AgRP neuron mediators GABA, NPY, and AgRP. *Cell Metab*
1505 2013;**18**:588–595.

1506 Kritzer MF, Adler A, Bethea CL. Ovarian hormone influences on the density of
1507 immunoreactivity for tyrosine hydroxylase and serotonin in the primate corpus striatum.
1508 *Neuroscience* 2003;**122**:757–772.

1509 Krug R, Benedict C, Born J, Hallschmid M. Comparable sensitivity of postmenopausal and
1510 young women to the effects of intranasal insulin on food intake and working memory. *J*
1511 *Clin Endocrinol Metab* 2010;**95**:E468–72.

1512 Kuk JL, Church TS, Blair SN, Ross R. Does measurement site for visceral and abdominal
1513 subcutaneous adipose tissue alter associations with the metabolic syndrome? *Diabetes*
1514 *Care* 2006;**29**:679–684.

1515 Lapid K, Lim A, Clegg DJ, Zeve D, Graff JM. Oestrogen signalling in white adipose
1516 progenitor cells inhibits differentiation into brown adipose and smooth muscle cells. *Nat*
1517 *Commun* 2014;**5**:5196.

1518 Le DSN, Pannacciulli N, Chen K, Salbe AD, Del Parigi A, Hill JO, Wing RR, Reiman EM,
1519 Krakoff J. Less activation in the left dorsolateral prefrontal cortex in the reanalysis of the
1520 response to a meal in obese than in lean women and its association with successful
1521 weight loss. *Am J Clin Nutr* 2007;**86**:573–579.

1522 Le Foll C, Dunn-Meynell AA, Miziorko HM, Levin BE. Regulation of hypothalamic neuronal
1523 sensing and food intake by ketone bodies and fatty acids. *Diabetes* 2014;**63**:1259–1269.

1524 Lee EB, Mattson MP. The neuropathology of obesity: insights from human disease. *Acta*
1525 *Neuropathol* 2014;**127**:3–28.

1526 Lee M-J, Wu Y, Fried SK. Adipose tissue heterogeneity: implication of depot differences in
1527 adipose tissue for obesity complications. *Mol Aspects Med* 2013;**34**:1–11.

1528 Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered
1529 body weight. *New England Journal of Medicine* 1995;**332**:621–628.

1530 Levin BE, Magnan C, Dunn-Meynell A, Le Foll C. Metabolic sensing and the brain: who,
1531 what, where, and how? *Endocrinology* 2011;**152**:2552–2557.

1532 Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in
1533 resistance to fat gain in humans. *Science* 1999;**283**:212–214.

1534 Levine JA. Nonexercise activity thermogenesis (NEAT): environment and biology. *Am J*
1535 *Physiol Endocrinol Metab* 2004;**286**:E675–85.

1536 Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat
1537 distribution. *Am J Clin Nutr* 1992;**55**:950–954.

1538 Légaré F, Godin G, Guilbert E, Laperrière L, Dodin S. Determinants of the intention to adopt
1539 hormone replacement therapy among premenopausal women. *Maturitas* 2000;**34**:211–
1540 218.

1541 Lê K-A, Mahurkar S, Alderete TL, Hasson RE, Adam TC, Kim JS, Beale E, Xie C, Greenberg
1542 AS, Allayee H, *et al.* Subcutaneous adipose tissue macrophage infiltration is associated
1543 with hepatic and visceral fat deposition, hyperinsulinemia, and stimulation of NF-κB
1544 stress pathway. *Diabetes* 2011;**60**:2802–2809.

1545 Li ET, Tsang LB, Lui SS. Resting metabolic rate and thermic effects of a sucrose-sweetened
1546 soft drink during the menstrual cycle in young Chinese women. *Can J Physiol Pharmacol*
1547 1999;**77**:544–550.

1548 Lim S, Wyker B, Bartley K, Eisenhower D. Measurement error of self-reported physical
1549 activity levels in New York City: assessment and correction. *Am J Epidemiol*
1550 2015;**181**:648–655.

1551 Lindholm A, Blomquist C, Bixo M, Dahlbom I, Hansson T, Sundström Poromaa I, Burén J. No
1552 difference in markers of adipose tissue inflammation between overweight women with
1553 polycystic ovary syndrome and weight-matched controls. *Human Reproduction*
1554 2011;**26**:1478–1485.

1555 Livingstone MB, Robson PJ, McCarthy S, Kiely M, Harrington K, Browne P, Galvin M,
1556 Wareham NJ, Rennie KL. Physical activity patterns in a nationally representative sample
1557 of adults in Ireland. *Public Health Nutr* 2001;**4**:1107–1116.

1558 Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S,
1559 Buchkovich ML, Yang J, *et al.* Genetic studies of body mass index yield new insights for
1560 obesity biology. *Nature* 2015;**518**:197–206.

1561 Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and
1562 decreased energy expenditure during the menopausal transition. *Int J Obes (Lond)*
1563 2008;**32**:949–958.

1564 López M, Tena-Sempere M. Estrogens and the control of energy homeostasis: a brain
1565 perspective. *Trends Endocrinol Metab* 2015;**26**:411–421.

1566 Lumeng CN, Deyoung SM, Bodzin JL, Saltiel AR. Increased inflammatory properties of
1567 adipose tissue macrophages recruited during diet-induced obesity. *Diabetes*
1568 2007;**56**:16–23.

1569 Lyons PM, Truswell AS, Mira M, Vizzard J, Abraham SF. Reduction of food intake in the
1570 ovulatory phase of the menstrual cycle. *Am J Clin Nutr* 1989;**49**:1164–1168.

1571 Madsen AM, El-Nashar SA, Hopkins MR, Khan Z, Famuyide AO. Endometrial ablation for the
1572 treatment of heavy menstrual bleeding in obese women. *Int J Gynaecol Obstet*
1573 2013;**121**:20–23.

1574 Mannerås-Holm L, Benrick A, Stener-Victorin E. Gene expression in subcutaneous adipose
1575 tissue differs in women with polycystic ovary syndrome and controls matched pair-wise
1576 for age, body weight, and body mass index. *Adipocyte* 2014;**3**:190–196.

1577 Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, Anderson
1578 G, Howard BV, Thomson CA, LaCroix AZ, *et al.* Menopausal hormone therapy and
1579 health outcomes during the intervention and extended poststopping phases of the
1580 Women's Health Initiative randomized trials. *JAMA* 2013;**310**:1353–1368.

1581 Manson JE, Kaunitz AM. Menopause Management--Getting Clinical Care Back on Track. *N*
1582 *Engl J Med* 2016;**374**:803–806.

1583 Marino L, Jornayvaz FR. Endocrine causes of nonalcoholic fatty liver disease. *World J*
1584 *Gastroenterol* 2015;**21**:11053–11076.

1585 Martínez de Morentin PB, González-García I, Martins L, Lage R, Fernández-Mallo D,
1586 Martínez-Sánchez N, Ruíz-Pino F, Liu J, Morgan DA, Pinilla L, *et al.* Estradiol regulates
1587 brown adipose tissue thermogenesis via hypothalamic AMPK. *Cell Metab* 2014;**20**:41–
1588 53.

1589 Matthews KA, Abrams B, Crawford S, Miles T, Neer R, Powell LH, Wesley D. Body mass
1590 index in mid-life women: relative influence of menopause, hormone use, and ethnicity. *Int*
1591 *J Obes Relat Metab Disord* 2001;**25**:863–873.

1592 Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance
1593 and glucose homeostasis. *Endocrine Reviews* 2013;**34**:309–338.

1594 Mauvais-Jarvis F. Estrogen and androgen receptors: regulators of fuel homeostasis and
1595 emerging targets for diabetes and obesity. *Trends Endocrinol Metab* 2011;**22**:24–33.

1596 McAllister JM, Modi B, Miller BA, Biegler J, Bruggeman R, Legro RS, Strauss JF.
1597 Overexpression of a DENND1A isoform produces a polycystic ovary syndrome theca
1598 phenotype. *Proceedings of the National Academy of Sciences* 2014;**111**:E1519–27.

1599 McCarthy MM, Arnold AP, Ball GF, Blaustein JD, De Vries GJ. Sex differences in the brain:
1600 the not so inconvenient truth. *J Neurosci* 2012;**32**:2241–2247.

1601 McCartney CR, Marshall JC. CLINICAL PRACTICE. Polycystic Ovary Syndrome. Solomon
1602 CG (ed). *N Engl J Med* 2016;**375**:54–64.

1603 McFadden KL, Cornier M-A, Melanson EL, Bechtell JL, Tregellas JR. Effects of exercise on
1604 resting-state default mode and salience network activity in overweight/obese adults.
1605 *Neuroreport* 2013;**24**:866–871.

1606 Melanson EL, Gavin KM, Shea KL, Wolfe P, Wierman ME, Schwartz RS, Kohrt WM.
1607 Regulation of energy expenditure by estradiol in premenopausal women. *J Appl Physiol*
1608 2015;**119**:975–981.

1609 Melanson KJ, Saltzman E, Russell R, Roberts SB. Postabsorptive and postprandial energy
1610 expenditure and substrate oxidation do not change during the menstrual cycle in young
1611 women. *J Nutr* 1996;**126**:2531–2538.

1612 Monteiro R, Teixeira D, Calhau C. Estrogen signaling in metabolic inflammation. *Mediators*
1613 *Inflamm* 2014;**2014**:615917–20.

1614 Moon JR, Stout JR, Walter AA, Smith AE, Stock MS, Herda TJ, Sherk VD, Young KC,
1615 Lockwood CM, Kendall KL, *et al.* Mechanical scale and load cell underwater weighing: a
1616 comparison of simultaneous measurements and the reliability of methods. *J Strength*
1617 *Cond Res* 2011;**25**:652–661.

1618 Morris JS, Dolan RJ. Involvement of human amygdala and orbitofrontal cortex in hunger-
1619 enhanced memory for food stimuli. *J Neurosci* 2001;**21**:5304–5310.

1620 Morrison SF, Madden CJ, Tupone D. Central neural regulation of brown adipose tissue
1621 thermogenesis and energy expenditure. *Cell Metab* 2014;**19**:741–756.

1622 Musatov S, Chen W, Pfaff DW, Mobbs CV, Yang X-J, Clegg DJ, Kaplitt MG, Ogawa S.
1623 Silencing of estrogen receptor alpha in the ventromedial nucleus of hypothalamus leads
1624 to metabolic syndrome. *Proc Natl Acad Sci USA* 2007;**104**:2501–2506.

NCD Risk factor Collaboration Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet* 2016; **387**:1377-1396.

Nelson VL, Legro RS, Strauss JF, McAllister JM. Augmented androgen production is a stable steroidogenic phenotype of propagated theca cells from polycystic ovaries. *Mol Endocrinol* 1999;**13**:946–957.

Nookaew I, Svensson P-A, Jacobson P, Jernås M, Taube M, Larsson I, Andersson-Assarsson JC, Sjöström L, Froguel P, Walley A, *et al.* Adipose tissue resting energy expenditure and expression of genes involved in mitochondrial function are higher in women than in men. *J Clin Endocrinol Metab* 2013;**98**:E370–8.

Norman RJ, Flight IH, Rees MC. Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution. *Cochrane Database Syst Rev* 2000:CD001018.

O'Rahilly S, Farooqi IS. Genetics of obesity. *Philos Trans R Soc Lond, B, Biol Sci* 2006;**361**:1095–1105.

Ode JJ, Pivarnik JM, Reeves MJ, Knous JL. Body mass index as a predictor of percent fat in college athletes and nonathletes. *Med Sci Sports Exerc* 2007;**39**:403–409.

ODPHP (Office of Disease Prevention and Health Promotion, US Dept Health and Human Services), Physical Activity Guidelines, Appendix 1, 2016. https://health.gov/paguidelines/

Ohlstein JF, Strong AL, McLachlan JA, Gimble JM, Burow ME, Bunnell BA. Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells. *J Mol Endocrinol* 2014;**53**:345–353.

Olofsson LE, Pierce AA, Xu AW. Functional requirement of AgRP and NPY neurons in ovarian cycle-dependent regulation of food intake. *Proceedings of the National Academy of Sciences* 2009;**106**:15932–15937.

Olszanecka-Glinianowicz M, Kuglin D, Dąbkowska-Huć A, Skałba P. Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2011;**154**:51–56.

Olszanecka-Glinianowicz M, Madej P, Nylec M, Owczarek A, Szanecki W, Skałba P, Chudek J. Circulating apelin level in relation to nutritional status in polycystic ovary syndrome and its association with metabolic and hormonal disturbances. *Clinical Endocrinology* 2013;**79**:238–242.

Oosthuyse T, Bosch AN. Oestrogen's regulation of fat metabolism during exercise and gender specific effects. *Curr Opin Pharmacol* 2012;**12**:363–371.

Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol* 2015;**402**:113–119.

Panotopoulos G, Ruiz JC, Raison J, Guy-Grand B, Basdevant A. Menopause, fat and lean distribution in obese women. *Maturitas* 1996;**25**:11–19.

Paolisso G, Rizzo MR, Mazziotti G, Rotondi M, Tagliamonte MR, Varricchio G, Carella C, Varricchio M. Lack of association between changes in plasma leptin concentration and in food intake during the menstrual cycle. *Eur J Clin Invest* 1999;**29**:490–495.

1670 Pardridge WM, Mietus LJ, Frumar AM, Davidson BJ, Judd HL. Effects of human serum on
1671 transport of testosterone and estradiol into rat brain. *Am J Physiol* 1980;**239**:E103–8.

1672 Pasarica M, Sereda OR, Redman LM, Albarado DC, Hymel DT, Roan LE, Rood JC, Burk
1673 DH, Smith SR. Reduced adipose tissue oxygenation in human obesity: evidence for
1674 rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response.
1675 *Diabetes* 2009;**58**:718–725.

1676 Pedersen SB, Kristensen K, Hermann PA, Katzenellenbogen JA, Richelsen B. Estrogen
1677 controls lipolysis by up-regulating alpha2A-adrenergic receptors directly in human
1678 adipose tissue through the estrogen receptor alpha. Implications for the female fat
1679 distribution. *J Clin Endocrinol Metab* 2004;**89**:1869–1878.

1680 Pelkman CL, Chow M, Heinbach RA, Rolls BJ. Short-term effects of a progestational
1681 contraceptive drug on food intake, resting energy expenditure, and body weight in young
1682 women. *Am J Clin Nutr* 2001;**73**:19–26.

1683 Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity
1684 after menopause. *Endocrine Reviews* 2002;**23**:90–119.

1685 Phelan S, Wyatt HR, Hill JO, Wing RR. Are the eating and exercise habits of successful
1686 weight losers changing? *Obesity (Silver Spring)* 2006;**14**:710–716.

1687 Phillips GB, Jing T, Heymsfield SB. Does insulin resistance, visceral adiposity, or a sex
1688 hormone alteration underlie the metabolic syndrome? Studies in women. *Metab Clin Exp*
1689 2008;**57**:838–844.

1690 Pichika R, Buchsbaum MS, Bailer U, Hoh C, Decastro A, Buchsbaum BR, Kaye W.
1691 Serotonin transporter binding after recovery from bulimia nervosa. *Int J Eat Disord*
1692 2012;**45**:345–352.

1693 Piers LS, Diggavi SN, Rijskamp J, van Raaij JM, Shetty PS, Hautvast JG. Resting metabolic
1694 rate and thermic effect of a meal in the follicular and luteal phases of the menstrual cycle
1695 in well-nourished Indian women. *Am J Clin Nutr* 1995;**61**:296–302.

1696 Pinnick KE, Neville MJ, Fielding BA, Frayn KN, Karpe F, Hodson L. Gluteofemoral adipose
1697 tissue plays a major role in production of the lipokine palmitoleate in humans. *Diabetes*
1698 2012;**61**:1399–1403.

1699 Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw
1700 YT, Spencer E, Moons KGM, Tjønneland A, *et al.* General and abdominal adiposity and
1701 risk of death in Europe. *N Engl J Med* 2008;**359**:2105–2120.

1702 Pohle-Krauza RJ, Carey KH, Pelkman CL. Dietary restraint and menstrual cycle phase
1703 modulated L-phenylalanine-induced satiety. *Physiol Behav* 2008;**93**:851–861.

1704 Polotsky HN, Polotsky AJ. Metabolic implications of menopause. *Semin Reprod Med*
1705 2010;**28**:426–434.

1706 Porcu P, Barron AM, Frye CA, Walf AA, Yang S-Y, He X-Y, Morrow AL, Panzica GC,
1707 Melcangi RC. Neurosteroidogenesis Today: Novel Targets for Neuroactive Steroid
1708 Synthesis and Action and Their Relevance for Translational Research. *J*
1709 *Neuroendocrinol* 2016;**28**.

Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;**73**:460–468.

Psilopanagioti A, Papadaki H, Kranioti EF, Alexandrides TK, Varakis JN. Expression of Adiponectin and Adiponectin Receptors in Human Pituitary Gland and Brain. *Neuroendocrinology* 2009;**89**:38–47.

Ramage LE, Akyol M, Fletcher AM, Forsythe J, Nixon M, Carter RN, van Beek EJR, Morton NM, Walker BR, Stimson RH. Glucocorticoids Acutely Increase Brown Adipose Tissue Activity in Humans, Revealing Species-Specific Differences in UCP-1 Regulation. *Cell Metab* 2016;**24**:130–141.

Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, Boyce V, Howard BV, Bogardus C. Reduced rate of energy expenditure as a risk factor for body-weight gain. *New England Journal of Medicine* 1988;**318**:467–472.

Ravussin Y, Leibel RL, Ferrante AW. A missing link in body weight homeostasis: the catabolic signal of the overfed state. *Cell Metab* 2014;**20**:565–572.

Reed GW, Hill JO. Measuring the thermic effect of food. *Am J Clin Nutr* 1996;**63**:164–169.

Reichborn-Kjennerud T, Bulik CM, Kendler KS, Røysamb E, Maes H, Tambs K, Harris JR. Gender differences in binge-eating: a population-based twin study. *Acta Psychiatr Scand* 2003;**108**:196–202.

Rock CL, Gorenflo DW, Drewnowski A, Demitrack MA. Nutritional characteristics, eating pathology, and hormonal status in young women. *Am J Clin Nutr* 1996;**64**:566–571.

Rogers NH, Perfield JW, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. *Endocrinology* 2009;**150**:2161–2168.

Rosen ED, Spiegelman BM. What we talk about when we talk about fat. *Cell* 2014;**156**:20–44.

Rosenbaum M, Leibel RL. Clinical review 107: Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. *J Clin Endocrinol Metab* 1999;**84**:1784–1789.

Rosenbaum M, Pietrobelli A, Vasselli JR, Heymsfield SB, Leibel RL. Sexual dimorphism in circulating leptin concentrations is not accounted for by differences in adipose tissue distribution. *Int J Obes Relat Metab Disord* 2001;**25**:1365–1371.

Rothemund Y, Preuschhof C, Bohner G, Bauknecht H-C, Klingebiel R, Flor H, Klapp BF. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* 2007;**37**:410–421.

Rubinow DR, Schmidt PJ. Gonadal steroids, brain, and behavior: role of context. *Dialogues Clin Neurosci* 2002;**4**:123–137.

Ruigrok ANV, Salimi-Khorshidi G, Lai M-C, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J. A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev* 2014;**39**:34–50.

1751 Rytka JM, Wueest S, Schoenle EJ, Konrad D. The portal theory supported by venous
1752 drainage-selective fat transplantation. *Diabetes* 2011;**60**:56–63.

1753 Saal Vom FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting
1754 chemical bisphenol A (BPA) and obesity. *Mol Cell Endocrinol* 2012;**354**:74–84.

1755 Sadarangani KP, Hamer M, Mindell JS, Coombs NA, Stamatakis E. Physical activity and risk
1756 of all-cause and cardiovascular disease mortality in diabetic adults from Great Britain:
1757 pooled analysis of 10 population-based cohorts. *Diabetes Care* 2014;**37**:1016–1023.

1758 Saito M. Brown adipose tissue as a regulator of energy expenditure and body fat in humans.
1759 *Diabetes Metab J* 2013;**37**:22–29.

1760 Salem V, Dhillo WS. IMAGING IN ENDOCRINOLOGY: The use of functional MRI to study
1761 the endocrinology of appetite. *Eur J Endocrinol* 2015;**173**:R59–68.

1762 Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, Burger HG, Colditz
1763 GA, Davis SR, Gambacciani M, *et al.* Postmenopausal hormone therapy: an Endocrine
1764 Society scientific statement. *J Clin Endocrinol Metab* 2010;**95**:s1–s66.

1765 Santosa S, Hensrud DD, Votruba SB, Jensen MD. The influence of sex and obesity
1766 phenotype on meal fatty acid metabolism before and after weight loss. *Am J Clin Nutr*
1767 2008;**88**:1134–1141.

1768 Santosa S, Jensen MD. The Sexual Dimorphism of Lipid Kinetics in Humans. *Front*
1769 *Endocrinol (Lausanne)* 2015;**6**:103.

1770 Schmidt PJ, Ben Dor R, Martinez PE, Guerrieri GM, Harsh VL, Thompson K, Koziol DE,
1771 Nieman LK, Rubinow DR. Effects of Estradiol Withdrawal on Mood in Women With Past
1772 Perimenopausal Depression: A Randomized Clinical Trial. *JAMA Psychiatry*
1773 2015;**72**:714–726.

1774 Schultz W. Neuronal Reward and Decision Signals: From Theories to Data. *Physiological*
1775 *Reviews* 2015;**95**:853–951.

1776 Schur EA, Kleinhans NM, Goldberg J, Buchwald D, Schwartz MW, Maravilla K. Activation in
1777 brain energy regulation and reward centers by food cues varies with choice of visual
1778 stimulus. *Int J Obes (Lond)* 2009;**33**:653–661.

1779 Shen W, Chen J, Gantz M, Velasquez G, Punyanitya M, Heymsfield SB. A single MRI slice
1780 does not accurately predict visceral and subcutaneous adipose tissue changes during
1781 weight loss. *Obesity (Silver Spring)* 2012;**20**:2458–2463.

1782 Shen W, Punyanitya M, Silva AM, Chen J, Gallagher D, Sardinha LB, Allison DB, Heymsfield
1783 SB. Sexual dimorphism of adipose tissue distribution across the lifespan: a cross-
1784 sectional whole-body magnetic resonance imaging study. *Nutr Metab (Lond)* 2009;**6**:17.

1785 Shen W, Wang Z, Punyanita M, Lei J, Sinav A, Kral JG, Imielinska C, Ross R, Heymsfield
1786 SB. Adipose tissue quantification by imaging methods: a proposed classification. *Obes*
1787 *Res* 2003;**11**:5–16.

1788 Shepard KN, Michopoulos V, Toufexis DJ, Wilson ME. Genetic, epigenetic and
1789 environmental impact on sex differences in social behavior. *Physiol Behav* 2009;**97**:157–
1790 170.

1791 Shin AC, Zheng H, Berthoud H-R. An expanded view of energy homeostasis: neural
1792 integration of metabolic, cognitive, and emotional drives to eat. *Physiol Behav*
1793 2009;**97**:572–580.

1794 Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, Strawbridge RJ,
1795 Pers TH, Fischer K, Justice AE, *et al.* New genetic loci link adipose and insulin biology to
1796 body fat distribution. *Nature* 2015;**518**:187–196.

1797 Silver HJ, Welch EB, Avison MJ, Niswender KD. Imaging body composition in obesity and
1798 weight loss: challenges and opportunities. *Diabetes Metab Syndr Obes* 2010;**3**:337–347.

1799 Small DM, Prescott J. Odor/taste integration and the perception of flavor. *Exp Brain Res*
1800 2005;**166**:345–357.

1801 Smith AW, Bosch MA, Wagner EJ, Rønnekleiv OK, Kelly MJ. The membrane estrogen
1802 receptor ligand STX rapidly enhances GABAergic signaling in NPY/AgRP neurons: role
1803 in mediating the anorexigenic effects of 17β-estradiol. *Am J Physiol Endocrinol Metab*
1804 2013;**305**:E632–40.

1805 Smith GI, Reeds DN, Okunade AL, Patterson BW, Mittendorfer B. Systemic delivery of
1806 estradiol, but not testosterone or progesterone, alters very low density lipoprotein-
1807 triglyceride kinetics in postmenopausal women. *J Clin Endocrinol Metab* 2014;**99**:E1306–
1808 10.

1809 Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, la Bretonne de J, Volafova J, Bray
1810 GA. Contributions of total body fat, abdominal subcutaneous adipose tissue
1811 compartments, and visceral adipose tissue to the metabolic complications of obesity.
1812 *Metab Clin Exp* 2001;**50**:425–435.

1813 Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and
1814 opposite associations of waist and hip circumferences with diabetes, hypertension and
1815 dyslipidemia: the AusDiab Study. *Int J Obes Relat Metab Disord* 2004;**28**:402–409.

1816 Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin*
1817 *Pharmacokinet* 2009;**48**:143–157.

1818 Sone M, Nagata H, Takekoshi S, Osamura RY. Expression and localization of leptin receptor
1819 in the normal rat pituitary gland. *Cell and tissue research* 2001;**305**:351–356.

1820 Sowers MF, Crutchfield M, Jannausch ML, Russell-Aulet M. Longitudinal changes in body
1821 composition in women approaching the midlife. *Ann Hum Biol* 1996;**23**:253–265.

1822 Spoletini I, Vitale C, Malorni W, Rosano GMC. Sex differences in drug effects: interaction
1823 with sex hormones in adult life. *Handb Exp Pharmacol* 2012;**214**:91–105.

1824 St-Onge M-P, Gallagher D. Body composition changes with aging: the cause or the result of
1825 alterations in metabolic rate and macronutrient oxidation? *Nutrition* 2010;**26**:152–155.

1826 Stensel D. Exercise, appetite and appetite-regulating hormones: implications for food intake
1827 and weight control. *Ann Nutr Metab* 2010;**57 Suppl 2**:36–42.

1828 Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-
1829 system activation in obese women in response to pictures of high-calorie foods.
1830 *Neuroimage* 2008;**41**:636–647.

1831 Stutzmann F, Tan K, Vatin V, Dina C, Jouret B, Tichet J, Balkau B, Potoczna N, Horber F,
1832 O'Rahilly S, *et al.* Prevalence of melanocortin-4 receptor deficiency in Europeans and
1833 their age-dependent penetrance in multigenerational pedigrees. *Diabetes* 2008;**57**:2511–
1834 2518.

1835 Sullivan EL, Daniels AJ, Koegler FH, Cameron JL. Evidence in female rhesus monkeys
1836 (Macaca mulatta) that nighttime caloric intake is not associated with weight gain. *Obes*
1837 *Res* 2005;**13**:2072–2080.

1838 Sullivan EL, Shearin J, Koegler FH, Cameron JL. Selective estrogen receptor modulator
1839 promotes weight loss in ovariectomized female rhesus monkeys (Macaca mulatta) by
1840 decreasing food intake and increasing activity. *Am J Physiol Endocrinol Metab*
1841 2012;**302**:E759–67.

1842 Sun K, Tordjman J, Clément K, Scherer PE. Fibrosis and adipose tissue dysfunction. *Cell*
1843 *Metab* 2013;**18**:470–477.

1844 Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in
1845 body composition and fat distribution in healthy women as measured by dual-energy X-
1846 ray absorptiometry. *Metab Clin Exp* 1995;**44**:369–373.

1847 Søndergaard E, Gormsen LC, Nellemann B, Jensen MD, Nielsen S. Body composition
1848 determines direct FFA storage pattern in overweight women. *Am J Physiol Endocrinol*
1849 *Metab* 2012;**302**:E1599–604.

1850 Taheri S, Murphy K, Cohen M, Sujkovic E, Kennedy A, Dhillo W, Dakin C, Sajedi A, Ghatei
1851 M, Bloom S. The effects of centrally administered apelin-13 on food intake, water intake
1852 and pituitary hormone release in rats. *Biochem Biophys Res Commun* 2002;**291**:1208–
1853 1212.

1854 Tai MM, Castillo TP, Pi-Sunyer FX. Thermic effect of food during each phase of the
1855 menstrual cycle. *Am J Clin Nutr* 1997;**66**:1110–1115.

1856 Tang QQ, Lane MD. Adipogenesis: from stem cell to adipocyte. *Annu Rev Biochem*
1857 2012;**81**:715–736.

1858 Tao Y-X. The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology.
1859 *Endocrine Reviews* 2010;**31**:506–543.

1860 Taylor RW, Grant AM, Williams SM, Goulding A. Sex differences in regional body fat
1861 distribution from pre- to postpuberty. *Obesity (Silver Spring)* 2010;**18**:1410–1416.

1862 Tchkonia T, Thomou T, Zhu Y, Karagiannides I, Pothoulakis C, Jensen MD, Kirkland JL.
1863 Mechanisms and metabolic implications of regional differences among fat depots. *Cell*
1864 *Metab* 2013;**17**:644–656.

1865 Tchoukalova YD, Votruba SB, Tchkonia T, Giorgadze N, Kirkland JL, Jensen MD. Regional
1866 differences in cellular mechanisms of adipose tissue gain with overfeeding. *Proceedings*
1867 *of the National Academy of Sciences* 2010;**107**:18226–18231.

1868 Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with
1869 psychological, reproductive and metabolic manifestations that impacts on health across
1870 the lifespan. *BMC Med* 2010;**8**:41.

1871 Tersigni C, Di Nicuolo F, D'Ippolito S, Veglia M, Castellucci M, Di Simone N. Adipokines:
1872 New Emerging Roles in Fertility and Reproduction. *Obstetrical \& Gynecological Survey*
1873 2011;**66**:47–63.

1874 Tobias JH, Steer CD, Vilarino-Güell C, Brown MA. Effect of an estrogen receptor-alpha intron
1875 4 polymorphism on fat mass in 11-year-old children. *J Clin Endocrinol Metab*
1876 2007;**92**:2286–2291.

1877 Tom SE, Cooper R, Patel KV, Guralnik JM. Menopausal characteristics and physical
1878 functioning in older adulthood in the National Health and Nutrition Examination Survey
1879 III. *Menopause* 2012;**19**:283–289.

1880 Torres-Leal FL, Fonseca-Alaniz MH, Rogero MM, Tirapegui J. The role of inflamed adipose
1881 tissue in the insulin resistance. *Cell Biochem Funct* 2010;**28**:623–631.

1882 Trémollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total
1883 and regional body composition changes in postmenopausal women. *Am J Obstet*
1884 *Gynecol* 1996;**175**:1594–1600.

1885 Vague J. La Differenciation Sexuelle Facteur Determinant Des Formes De Lobesite. *Presse*
1886 *Medicale* 1947;**55**:339–340.

1887 Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel LE, Alonso-Alonso M,
1888 Audette M, Malbert CH, Stice E. Neuroimaging and neuromodulation approaches to
1889 study eating behavior and prevent and treat eating disorders and obesity. *Neuroimage*
1890 *Clin* 2015;**8**:1–31.

1891 Valette M, Bellisle F, Carette C, Poitou C, Dubern B, Paradis G, Hercberg S, Muzard L,
1892 Clément K, Czernichow S. Eating behaviour in obese patients with melanocortin-4
1893 receptor mutations: a literature review. *Int J Obes (Lond)* 2013;**37**:1027–1035.

1894 van der Sluis IM, Boot AM, Krenning EP, Drop SLS, de Muinck Keizer-Schrama SMPF.
1895 Longitudinal follow-up of bone density and body composition in children with precocious
1896 or early puberty before, during and after cessation of GnRH agonist therapy. *J Clin*
1897 *Endocrinol Metab* 2002;**87**:506–512.

1898 Van Pelt RE, Dinneno FA, Seals DR, Jones PP. Age-related decline in RMR in physically
1899 active men: relation to exercise volume and energy intake. *Am J Physiol Endocrinol*
1900 *Metab* 2001;**281**:E633–9.

1901 Van Pelt RE, Gavin KM, Kohrt WM. Regulation of Body Composition and Bioenergetics by
1902 Estrogens. *Endocrinol Metab Clin North Am* 2015;**44**:663–676.

1903 Vieira Potter VJ, Strissel KJ, Xie C, Chang E, Bennett G, Defuria J, Obin MS, Greenberg AS.
1904 Adipose tissue inflammation and reduced insulin sensitivity in ovariectomized mice
1905 occurs in the absence of increased adiposity. *Endocrinology* 2012;**153**:4266–4277.

1906 Villa J, Pratley RE. Adipose tissue dysfunction in polycystic ovary syndrome. *Curr Diab Rep*
1907 2011;**11**:179–184.

1908 Vogel CIG, Boes T, Reinehr T, Roth CL, Scherag S, Scherag A, Hebebrand J, Hinney A.
1909 Common variants near MC4R: exploring gender effects in overweight and obese children
1910 and adolescents participating in a lifestyle intervention. *Obes Facts* 2011;**4**:67–75.

1911 Votruba SB, Jensen MD. Sex differences in abdominal, gluteal, and thigh LPL activity. *Am J*
1912 *Physiol Endocrinol Metab* 2007;**292**:E1823–8.

1913 Wang G-J, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR,
1914 Geliebter A, *et al.* Exposure to appetitive food stimuli markedly activates the human
1915 brain. *Neuroimage* 2004;**21**:1790–1797.

Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PWF, Sutherland P, Omland T, Vasan RS. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002;**90**:254–258.

Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005;**81**:555–563.

Wang Z, Ying Z, Bosy-Westphal A, Zhang J, Heller M, Later W, Heymsfield SB, Müller MJ. Evaluation of specific metabolic rates of major organs and tissues: comparison between men and women. *Am J Hum Biol* 2011;**23**:333–338.

Wolters B, Lass N, Reinehr T. Treatment with gonadotropin-releasing hormone analogues: different impact on body weight in normal-weight and overweight children. *Hormone Research in Paediatrics* 2012;**78**:304–311.

Woolf K, Reese CE, Mason MP, Beaird LC, Tudor-Locke C, Vaughan LA. Physical activity is associated with risk factors for chronic disease across adult women's life cycle. *J Am Diet Assoc* 2008;**108**:948–959.

Xu P, Cao X, He Y, Zhu L, Yang Y, Saito K, Wang C, Yan X, Hinton AO, Zou F, *et al.* Estrogen receptor-α in medial amygdala neurons regulates body weight. *J Clin Invest* 2015;**125**:2861–2876.

Xu Y, Nedungadi TP, Zhu L, Sobhani N, Irani BG, Davis KE, Zhang X, Zou F, Gent LM, Hahner LD, *et al.* Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. *Cell Metab* 2011;**14**:453–465.

Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;**93**:162–168.

Yu Z, Geary N, Corwin RL. Individual effects of estradiol and progesterone on food intake and body weight in ovariectomized binge rats. *Physiol Behav* 2011;**104**:687–693.

Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, *et al.* Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 2005;**366**:1640–1649.

Zeleznik AJ, Pohl CR. Control of follicular development, corpus luteal function, the maternal recognition of pregnancy, and the neuroendocrine regulation of the menstrual cycle in higher primates. In: Niell JD, editor, Knobil and Neill's Physiology of Reproduction (3rd ed.). Amsterdam, The Netherlands: Elsevier/Academic, 2006, p. 2449-2510.

Zhu Y, Bond J, Thomas P. Identification, classification, and partial characterization of genes in humans and other vertebrates homologous to a fish membrane progestin receptor. *Proc Natl Acad Sci USA* 2003;**100**:2237–2242.

Figure 1

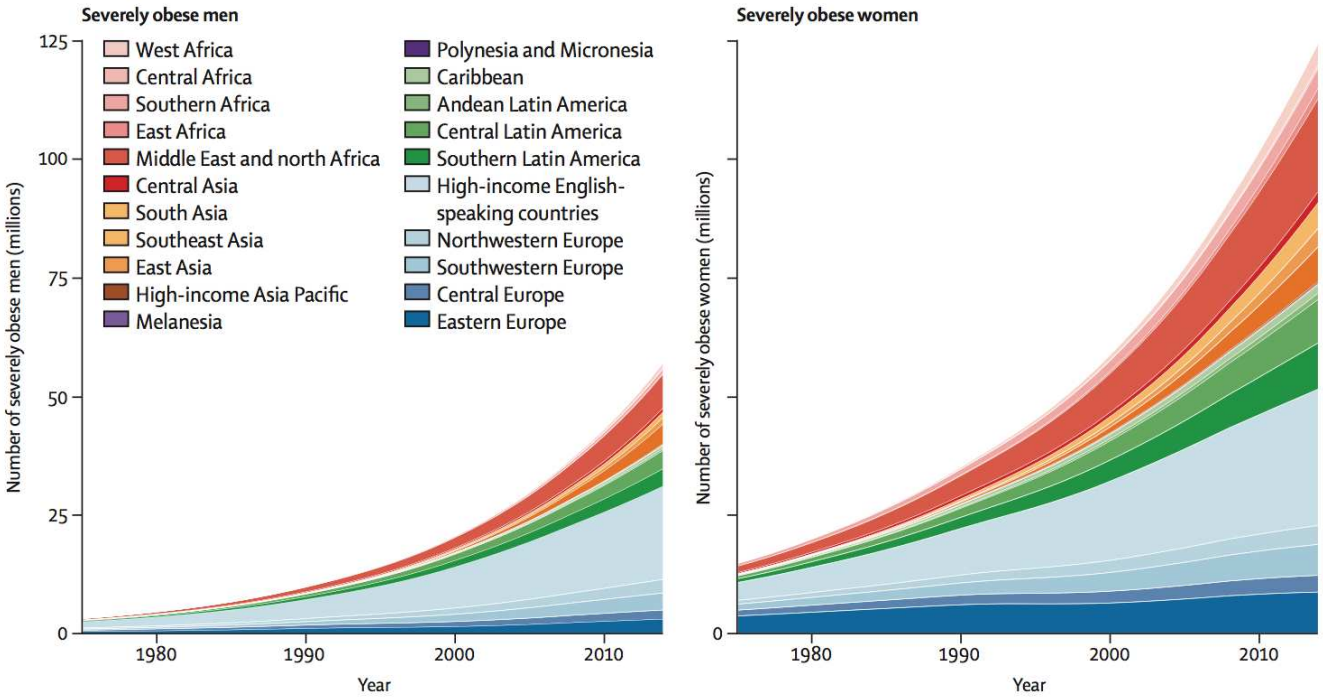
Severely obese men
West Africa
Central Africa
Southern Africa
East Africa
Middle East and north Africa
Central Asia
South Asia
Southeast Asia
East Asia
High-income Asia Pacific
Melanesia
Polynesia and Micronesia
Caribbean
Andean Latin America
Central Latin America
Southern Latin America
High-income English-speaking countries
Northwestern Europe
Southwestern Europe
Central Europe
Eastern Europe
Number of severely obese men (millions)
125
100
75
50
25
0
1980
1990
2000
2010
Year
Severely obese women
Number of severely obese women (millions)
0
1980
1990
2000
2010
Year

Figure 2

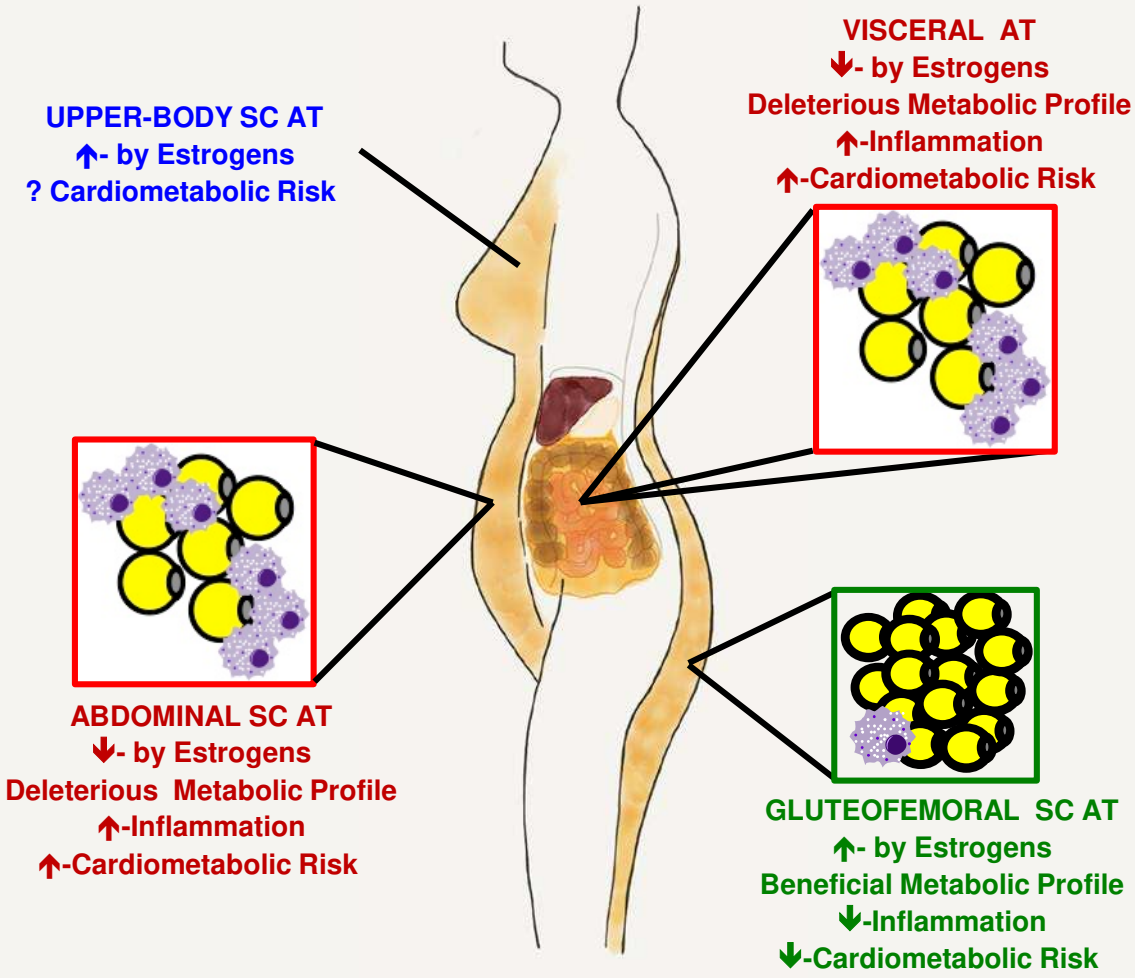
UPPER-BODY SC AT
↑- by Estrogens
? Cardiometabolic Risk
VISCERAL AT
↓- by Estrogens
Deleterious Metabolic Profile
↑-Inflammation
↑-Cardiometabolic Risk
ABDOMINAL SC AT
↓- by Estrogens
Deleterious Metabolic Profile
↑-Inflammation
↑-Cardiometabolic Risk
GLUTEOFEMORAL SC AT
↑- by Estrogens
Beneficial Metabolic Profile
↓-Inflammation
↓-Cardiometabolic Risk

Figure 3

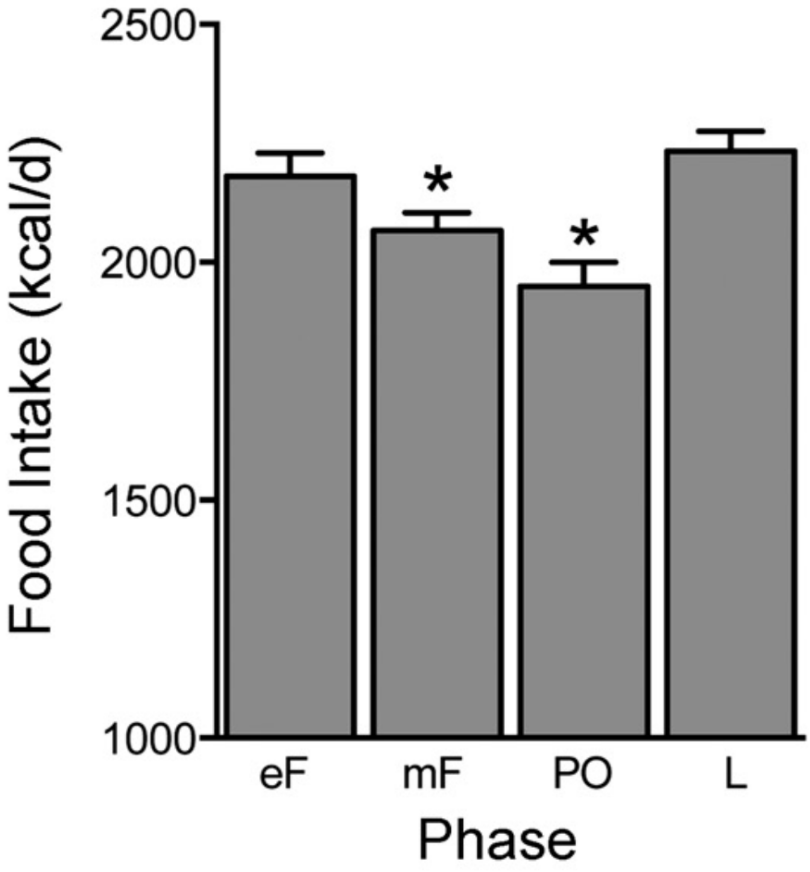

Figure 4

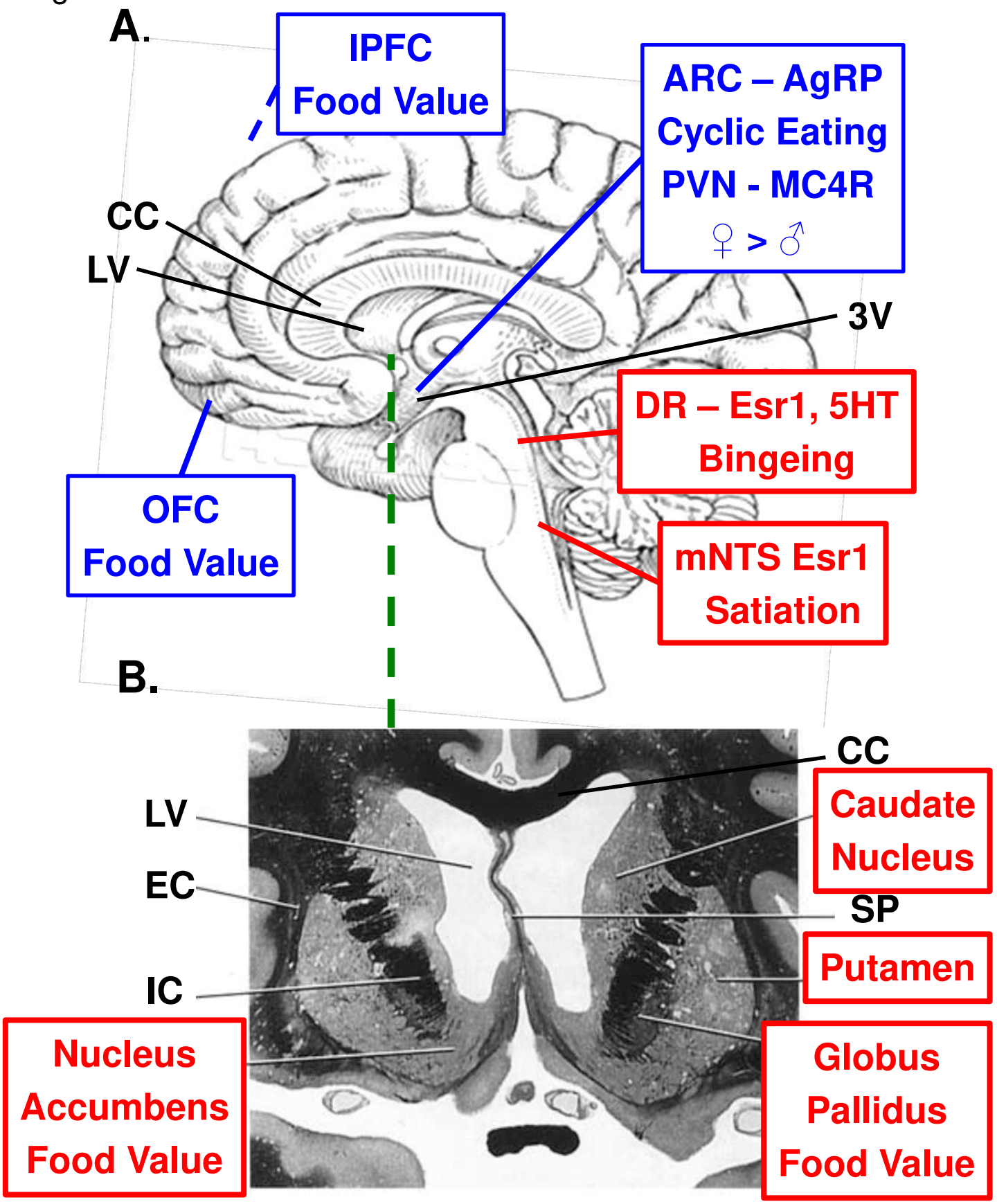
A.
IPFC
Food Value
ARC – AgRP
Cyclic Eating
PVN - MC4R
♀ > ♂
CC
LV
3V
DR – Esr1, 5HT
Bingeing
OFC
Food Value
mNTS Esr1
Satiation
B.
CC
Caudate
Nucleus
LV
EC
SP
Putamen
IC
Nucleus
Accumbens
Food Value
Globus
Pallidus
Food Value

Figure 5

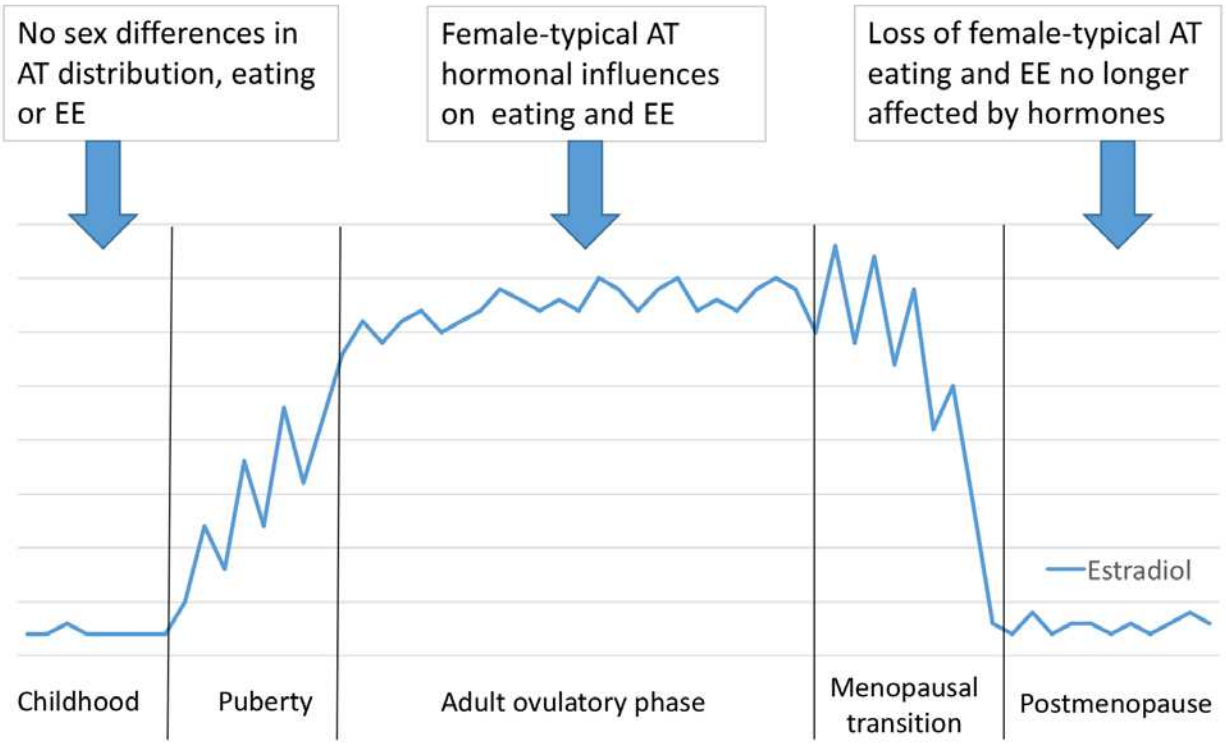
No sex differences in AT distribution, eating or EE
Female-typical AT hormonal influences on eating and EE
Loss of female-typical AT eating and EE no longer affected by hormones
Estradiol
Childhood
Puberty
Adult ovulatory phase
Menopausal transition
Postmenopause

Table 1. Menopause-associated increases in adiposity, measured with DEXA or CT and dissociated from the effect of aging with multiple-regression analysis.

Study	Lean Mass (kg)		Fat mass (kg)		% Fat	
Menopausal status :	**Pre-**	**Post-**	**Pre-**	**Post-**	**Pre-**	**Post**
Panotopoulos et al. (1996)	43	41*	30	31*	~41	~44*
Ley et al. (1992)	38±3	38±3	19±6	23±5*	32	36*
Trémollieres et al. (1996)	36±3	36±3[a]	18±5	18±5[a]	32	32[a]
		35±3[b]*		20±5[b]*		35[b]*
Phillips et al. (2008)	41	37	22±1	32±2*	~35	~46
Svendsen et al. (1995)	Δ = -4.0*		Δ = +3.1*		Δ = +5.4±1.6*	

Data are means ± SEM; lean mass does not include bone; ~ indicates estimated from data given. Subject characteristics (mean ± SD) were: **(Panotopoulos *et al.*, 1996)**: French women, 26 premenopausal, aged 43 ± 4 y, BMI 31 ± 3 kg/m^2, and 73 postmenopausal, aged 54 ± 4 y, BMI 31 ± 4 kg/m^2; data are sums of arms, trunk and legs, not whole body; variabilities of sums not given; Ley et al **(Ley *et al.*, 1992)**: British women, 61 premenopausal, aged 32 ± 6 y, BMI 22 ± 2 kg/m^2, and 70 postmenopausal, aged 53 ± 5 y, BMI 24 ± 2 kg/m^2; **(Trémollieres *et al.*, 1996)**: French women, 68 premenopausal, aged 49 ± 3 y, BMI 22 ± 2 kg/m^2, [a]100 younger postmenopausal, aged 54 ± 3 y, BMI 22 ± 2 kg/m^2, and [b]37 older postmenopausal, aged 64 ± 4 y, BMI 23 ± 2 kg/m^2; **(Phillips *et al.*, 2008)**: US American women, 58 premenopausal, aged 39 ± 1 y, BMI 24 ± 1 kg/m^2, and 20 postmenopausal, aged 61 ± 2 y, BMI 28 ± 1 kg/m^2, not all variability or statistics reported; **(Svendsen *et al.*, 1995)**: Swedish women collated by age decade; overall n = 407, age range 18-80 y, mean BMI per decade, ~22 - 25 kg/m^2.; data are estimated menopause effect (Δ). *Significant menopause effect.

Table 2. Sex differences and effects of estrogens on adiposity, eating, and EE in women

Adiposity

- ◆ Beginning at puberty, positive energy balance leads to female-typical AT distribution, i.e., greater accretion of gluteofemoral subcutaneous AT and less accretion of visceral AT.
- ◇ Estrogens and adipocyte genes synergize to produce female-typical AT distribution.
- ◇ Loss of estrogens after menopause increases total adiposity and decreases lean body mass, and estrogenic HT prevents this.
- ◇ Loss of estrogens after menopause partially reverses female-typical regional AT distribution, and estrogenic HT prevents this.

Eating

- ◆ Increasing estrogen secretion through the follicular phase progressively reduces daily food intake.
- ○ Estrogens act on Esr1-expressing neurons in the cmNTS to increase CCK-mediated satiation; several other meal-control mechanisms may participate.
- ◇ Sex differences in gustatory sensory function affect eating
- ◆ Genetic defects in brain α-MSH–MC4R signalling lead to a more marked overeating and obesity syndrome in females than males.
- ◇ Neuroimaging studies indicate that estrogens increase the activity of striatal dopaminergic neurons that processing of flavour hedonics.
- ◇ Neuroimaging studies indicate that estrogens increase lateral prefrontal cortex processing of cognitive controls inhibiting eating.

EE

- ◇ Estrogens increase REE during the luteal phase.
- ○ Estrogens act in several brain sites to increase physical activity EE in rats and mice.

Note: ◆ indicates well established effects in humans with proven or likely clinical relevance, as reviewed in text; ◇ indicates effects apparent effects in humans with as yet uncertain clinical relevance; ○ indicates effects established in animal research. Abbreviations: α-MSH α-melanocyte-stimulating hormone; MC4R, melanocortin 4 receptor.